

Palladium-Catalyzed Carboamination and Carboetherification Reactions for the Synthesis
of Heterocycles

by

Josephine S. Nakhla

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Chemistry)
in The University of Michigan
2008

Doctoral Committee:

Assistant Professor John P. Wolfe, Chair
Professor John R. Traynor
Professor Edwin Vedejs
Associate Professor Melanie S. Sanford

© Josephine S. Nakhla

All rights reserved

2008

To My Family

Acknowledgements

First and foremost, I would like to thank my advisor, Dr. John Wolfe. In the five years I spent at Michigan, I have learned so much from Dr. Wolfe, about chemistry and about the world. I am not sure that is the role an advisor expects to play in a student's life, but I grew up here and I think I owe much of that to him. Dr. Wolfe taught me how to solve problems and that even if I couldn't answer quite right that there was a way to reason through things and sometimes especially in cases where the answer is not clear, that is almost better. There is a method. He taught me that sometimes though you want the world, sometimes you have to settle for just a piece. I think this is a valuable lesson—we come in raw and immature and we come out learned (or at least more so). There were nights I wanted to shove my head in the hood as I ran my column or jump out the window by my desk (I think I told him some of those times). But I did not. He taught me how sometimes you have to have strength even if you do not want to and that if I was having too much fun, I wasn't doing it right (he never said that but I learned it). You taught me discipline and how to be accountable. Perhaps I had the foundation from somewhere from inside myself but you helped lay everything else. Dr. Wolfe's knowledge amazes me and is a lesson too, that learning doesn't really stop at some point because we finished classes, or are no longer being formally tested on chemistry. I want to also thank Dr. Wolfe for proofreading this thesis exhaustively. Your perfectionism is

incredible and it will not be forgotten. You will never know the amount of respect and admiration I have for you. I am forever changed by the role you played in my life.

I want to thank Dr. Myra Bertrand, who taught me a lot about life and chemistry. I am glad I met you, Myra. We have had some good times. There were more difficult ones for both of us and I am glad you were there. You always put things in perspective and I can appreciate that. You always encouraged me, which is important to me because I didn't always want to keep going. I remember a few years back you said "this is a big thing we are doing—perhaps the biggest." I think sometimes one wants to forget that while we are doing it because we try to live day by day and not think this is going to keep going, but at the end, you want to hear it. Thank you for your support over the years and for proofreading a portion of this work.

I would like to thank my committee members, Dr. Melanie Sanford, Dr. John Traynor, and Dr. Edwin Vedejs for agreeing to be on my committee and for various interactions over the years.

Dr. Sanford has been an incredible source for me. I have admired her from the first day I met her at the recruitment weekend when we all went to dinner at Real Seafood. I remember having heard stories about how incredibly lucky I was to be going to Michigan where both John and Melanie were starting out and how sought-after they were. I have had the pleasure of attending group meetings with Melanie and her students and I really must say, I have learned a great deal from them. The physical organic chemistry course was outstanding (but not easy!). I think Dr. Sanford, that you are quite the inspiration, obviously to people in science and as a person and I am happy that we crossed paths for I learned a great deal.

I thank Dr. Traynor for taking the time to be on my committee and for always asking insightful questions. I very much enjoyed the course you taught as well (Pharmacology). I thank you for your support and kind words over the years.

I know whenever Dr. Vedejs asks a question or when he is teaching a class, that there is always something more to it. One thinks they got it but what they do not realize is that Dr. Vedejs is actually thinking about it on a completely different level, a much deeper level. He is always very patient though with the student and I am very grateful to have had the opportunity to be a student of yours. The mechanisms' class was fantastic and when I think about how a reaction is working, I sometimes think back to Dr. Vedejs' comment about how he regularly goes back and reads Grossman's text. If a brilliant man can go back and read the introductory organic text than there is no shame for me to return to it and brush up on those first principles. I have appreciated his feedback over the years. Presenting at your group meeting was very useful to me as well in terms of providing me with a different perspective on the chemistry and I am very grateful for that.

I would also like to thank my husband, Dr. Steve Caskey. While we met in graduate school, we both understood the importance of focusing on the science in this particular period of our life and we made it work. I am forever indebted to him for his support and patience with me during this time. Your knowledge and my curiosity make us an interesting team, me always asking questions and you coming with some pretty good answers. I wish I could say we don't talk about chemistry, but that is not realistic. The fact is it is a huge part of our lives. I have learned a great amount from you, Steve, in terms of chemistry and about life. And I will always love you.

I would like to thank my father, Saad Nakhla for his support and love over the last 27 years of my life and for making sacrifices for me that cannot possibly be repaid. You are a wonderful, honorable man and I am so lucky to have had and to have you in my life. I wonder sometimes what would have been my fate had you not been the person you are. I don't think I would be writing this. You always supported me—whatever I wanted to do—you supported me. And don't think for one minute I don't know what you went through. I know it was not easy and I know how much your love of me guided you. Raising a teenager by yourself who wanted to find herself and learn about the world was difficult. I know and understand this now and my respect for you is unmatched. I have always admired your strength and I am very proud to be your daughter. For this and for raising me and for everything you have given me in this life, I am eternally grateful and you have my never-ending love, support, and respect. I write all this knowing that you brought me to this point—none of this would have been possible without you. I get my strength to forge ahead from you—I always have.

I want to thank my wonderful father and mother-in law. Over the last few years we have become very close. You both have given me so much support and love that I surely could not have completed this without you. I thank my sister-in-law and her husband, Anisa and Tony Dunn for their support and for going to law school an hour away so we can enjoy the occasional glass of champagne which usually landed on your couch. We have enjoyed many good times and I look forward to many more!

I would like to thank my original organic chemistry teacher and professor, mentor and advisor, Professor Kevin Shea at Smith College. I still remember one of his first days as a professor at Smith College and his announcement for students interested in summer

research and I thought, this person is motivated and enthusiastic, how could I not consider this opportunity. I am glad I did. Chemistry is frustrating most of the time, but when it works...or when you get it...

I'd like to thank Jeff Kampf for solving (I believe it was 11) crystal structures for me. It was really a great pleasure working with him in those first few years and I am very grateful for his hard work and incredible efficiency! I also want to thank Eugenio Alvarado and Chris Kojiro for their help with various NMR experiments and questions over the years.

I would also like to thank my labmates in the Wolfe group—Dr. Josh Ney and Dr. Mike Hay, who both played a large role in my joining the lab and always encouraged me. I learned to think about chemistry in a different way because of them. I want to thank Natalie Giampietro for her friendship and various chemistry discussions. You have a very bright future—just keep going. You are probably one of the few people in the building who understands my love of fine handbags. I have enjoyed our time together Natalie, and I know you will be a great success. I have enjoyed many great conversations with my benchmate Georgia Lemen, who was born to teach. You will be a remarkable professor one day. I would also like to thank the remainder of the Wolfe lab, including Jonathan Fritz, Joshua Neukom, Peter Mai, Nikki Guthrie, Ahleah Rohr, Matthew Leathen, Dani Schultz and Amanda Ward. You are all very talented people and I wish you all the best in chemistry and in life.

Dipa Kalyani and Lopa Desai (Sanford Lab) have been exceedingly supportive of me through this process and I have been honored to have met you. You both are

incredible chemists and I have learned so much from both of you. Thank you for your friendship and support over the years. I will never forget it or either of you.

I would like to thank my advisor for his support financially over the years as well. The studies described in chapters 2-4 were supported by the National Institute of Health NIGMS under Grant No. GM-071650. The studies described in chapter 5 were supported by the National Science Foundation under Grant No. 0705290.

Last but not least, I want to thank my mother. I cannot say you have been there for me to talk or help get me through this. You were never physically there. I spent a lot of time mad about this. I probably still am. I did not get to know you the way I would have liked. But somehow I feel I know you better than anyone. I remember no matter what was going on in your life, you always loved me above anything else. And I remember your passion about life, about everything. This passion did not die with you. It lives on in me and it propels me forward—everyday. This is for you.

“The battle of life is, in most cases, fought uphill; and to win it without a struggle were perhaps to win it without honor. If there were no difficulties there would be no success; if there were nothing to struggle for, there would be nothing to be achieved.”

Samuel Smiles (Scottish Author 1812-1904)

TABLE OF CONTENTS

DEDICATION.....	ii
ACKNOWLEDGEMENTS	iii
LIST OF SCHEMES	x
LIST OF FIGURES	xv
LIST OF TABLES	xvii
LIST OF ABBREVIATIONS	xix
ABSTRACT.....	xxii

PART ONE

Pd-Catalyzed Carboamination Reactions: Synthesis of Piperidines and Piperazines

CHAPTER

I. Synthesis of Pyrrolidines and Tetrahydrofurans via Pd-Catalyzed Carboamination and Carboetherification Reactions of γ -Hydroxy and γ -Amino Alkenes with Aryl and Alkenyl Bromides.....	1
II. Carboamination Reactions for the Synthesis of Piperidines	13
III. Carboamination Reactions for the Asymmetric Synthesis of Piperazines.....	54

PART TWO

Intramolecular Pd-Catalyzed Carboetherification and Carboamination Reactions for the Synthesis of Tetrahydrofurans and Pyrrolidines

CHAPTER

IV. Intramolecular Pd-Catalyzed Carboetherification and Carboamination Reactions.....	157
V. Stoichiometric Studies Towards the Synthesis of Likely Intermediates in Intramolecular Pd-Catalyzed Carboetherification and Carboamination Reactions.....	275

LIST OF SCHEMES

Scheme 1. Proposed Catalytic Cycle for Pd-Catalyzed Carboamination Reaction	3
Scheme 2. Origin of Side Products in Pd-Catalyzed Carboamination Reactions.....	5
Scheme 3. Stereochemical Model for Pd-Catalyzed Intermolecular Carboamination Reactions	6
Scheme 4. Mechanism of Pd-Catalyzed Intermolecular Carboetherification Reaction ..	7
Scheme 5. Mechanism of Pd-Catalyzed Anti-Aminocarbonylation Reaction.....	8
Scheme 6. Mechanism of Pd-Catalyzed Anti-Oxycarbonylation Reaction.....	8
Scheme 7. Intramolecular Cu-Mediated Carboamination Reactions Providing Syn- Addition Products	9
Scheme 8. Carboamination Reactions for the Synthesis of 2-Vinyl Piperidines.....	17
Scheme 9. Hydroamination Reactions for the Synthesis of Piperidines.....	18
Scheme 10. Synthesis of δ -(<i>N</i> -Phenylamino) Alkenes	19
Scheme 11. Synthesis of δ -(<i>N</i> -Boc-amino) and δ -(<i>N-p</i> -Cyanophenyl-amino) Alkenes..	20
Scheme 12. Synthesis of α -Phenyl-Substituted δ -(<i>N</i> -Boc-amino) and δ -(<i>N-p</i> - Cyanophenyl-amino) Alkenes	21
Scheme 13. Synthesis of α -Methyl-Substituted δ -(<i>N</i> -Boc-amino) Alkenes.....	21
Scheme 14. Proposed Catalytic Cycle for Piperidine Formation	34
Scheme 15. Origin of <i>N</i> -Arylation Side Product (II-56)	35
Scheme 16. Origin of Side Products II-57 and II-58	36
Scheme 17. Formation of <i>N</i> -Arylation Side Product II-74 from Decomposition of	

II-33	37
Scheme 18. Formation of Heck Side Product II-73 from II-33	38
Scheme 19. Synthesis of 2,6-Dimethyl Piperazines	56
Scheme 20. Synthesis of 2,6-Disubstituted Piperazines	57
Scheme 21. Synthesis of N^1,N^1 -Diallyl- N^2 -Phenylethane-1,2-Diamine	59
Scheme 22. Synthesis of Monosubstituted Piperazines	60
Scheme 23. Synthesis of Monosubstituted Boc-Piperazines	61
Scheme 24. Retrosynthetic Analysis for 2,6-Disubstituted Piperazines.....	62
Scheme 25. Synthesis of Substrates for 2,6-Disubstituted Piperazine Synthesis I.....	65
Scheme 26. Synthesis of Substrates for 2,6-Disubstituted Piperazine Synthesis II.....	66
Scheme 27. Proposed Catalytic Cycle for Piperazine Formation	74
Scheme 28. Origin of Side Products in Piperazine-Forming Reactions	76
Scheme 29. Explanation of Stereochemistry for 2,5- <i>Cis</i> -Disubstituted Pyrrolidine- Forming Carboamination Reactions	78
Scheme 30. Explanation of Stereochemistry for 2,6- <i>Cis</i> -Disubstituted Piperazine- Forming Carboamination Reactions	79
Scheme 31. Synthesis of 2,6-Disubstituted Piperazines Via Hydroamination	82
Scheme 32. Retrosynthetic Analysis for 2,3-Disubstituted Piperazines.....	85
Scheme 33. Synthesis of Substrates for 2,3-Disubstituted Piperazine Synthesis	85
Scheme 34. Explanation of Stereochemistry for 2,3- <i>Trans</i> -Disubstituted Piperazine- Forming Carboamination Reactions	87
Scheme 35. Synthesis of Cyclic Olefin Substrate III-153	88
Scheme 36. Synthesis of Phenylene-Diamine Substrates	89

Scheme 37. Intramolecular Syn-Oxy- or Amino-palladation Mechanism	159
Scheme 38. Intramolecular Anti-Oxy- or Amino-palladation Mechanism	160
Scheme 39. Synthesis of (+)-Testudinariol A (IV-20) (Mori).....	162
Scheme 40. Synthesis of (+)-Testudinariol A Part I (Montgomery)	163
Scheme 41. Synthesis of (+)-Testudinariol A Part II (Montgomery)	164
Scheme 42. Intramolecular Wacker-Type Carbopalladation Reactions	166
Scheme 43. Substrate Synthesis for Intramolecular Carboetherification and Carboamination Reactions-Synthesis of Key Intermediates IV-46 and IV-47 ...	168
Scheme 44. Substrate Synthesis of <i>E</i> -Hydroxy Alkenes-Synthesis of IV-48 , IV-49 , IV-50	169
Scheme 45. Substrate Synthesis of <i>E</i> -Amino Alkenes-Synthesis of IV-52 , IV-55	170
Scheme 46. Substrate Synthesis of <i>Z</i> -Hydroxy Alkenes-Synthesis of IV-56 , IV-57 , IV-58	170
Scheme 47. Substrate Synthesis of <i>Z</i> -Amino Alkenes-Synthesis of IV-60 , IV-63	171
Scheme 48. Products of Pd-Catalyzed Carboetherification of IV-56	174
Scheme 49. Proof of Stereochemistry-Preparation and X-ray Structure of IV-75	175
Scheme 50. Intramolecular Carboetherification of IV-56 and IV-48	177
Scheme 51. Intramolecular Carboetherification of IV-50 and IV-58	179
Scheme 52. Proof of Stereochemistry-Preparation and X-ray Structure of IV-81	183
Scheme 53. Preparation of Compound IV-87	188
Scheme 54. Proof of Stereochemistry-Preparation and X-ray Structure of IV-88	188
Scheme 55. Preparation of Compound IV-92	193
Scheme 56. Preparation of Compound IV-94	193

Scheme 57. Proof of Stereochemistry-Preparation and X-ray Structure of IV-95	194
Scheme 58. Proof of Stereochemistry-Preparation and X-ray Structure of IV-96	195
Scheme 59. Synthesis of Boc-Amine IV-99	195
Scheme 60. Preparation of IV-107 and Proof of Stereochemistry-Preparation and X-ray Structure of IV-108	199
Scheme 61. Proof of Stereochemistry-Preparation and X-ray Structure of IV-110	200
Scheme 62. Rationale for Syn-Addition Products	206
Scheme 63. Alternate Mechanism for Syn-Addition Products (Pd–C Bond Insertion) ..	208
Scheme 64. Intermolecular Probe: Rate of Pd–C vs. Pd–O Bond Insertion	209
Scheme 65. Formation of Anti-Addition Products from β -Hydride Elimination/Reinsertion/ σ -Bond Rotation Pathway	211
Scheme 66. Formation of Anti-Addition Products: Wacker and Heck-Type Mechanisms	213
Scheme 67. Anti-Amino-Palladation for the Synthesis of Boc-Protected Pyrrolidines ..	216
Scheme 68. Substrate Synthesis of Esters IV-161 and IV-162	218
Scheme 69. Formation of IV-167 Via Decomposition of IV-163	220
Scheme 70. Synthesis of IV-175	221
Scheme 71. Synthesis of IV-179	223
Scheme 72. Synthesis of IV-184 and IV-186	224
Scheme 73. Synthesis and Carboetherification of IV-191 to IV-192	227
Scheme 74. Proposed Mechanism for Carboetherification/Carboamination Reaction Providing Products Resulting in Syn-Addition Across Olefin of Substrate V-1	276

Scheme 75. Proposed Mechanism for Conversion of V-7 to V-15 (Syn-Addition).....	291
Scheme 76. Proposed Mechanism for Conversion of V-7 to V-14 (Anti-Addition).....	293

LIST OF FIGURES

Figure 1. Biologically Active Piperidine Natural Products and Pharmaceuticals	14
Figure 2. Piperazine Pharmaceuticals	55
Figure 3. Synthetically Challenging Substituted Piperazines	56
Figure 4. Comparison of β -hydride Elimination Products in Six- Vs. Five-Membered Rings	77
Figure 5. Proposed Twist Boat Conformation for Hydroamination Reactions	83
Figure 6. Natural Products containing Heterocycles with Attached Carbocycles	161
Figure 7. Side Products in Pd-Catalyzed Carboamination Reactions	192
Figure 8. Comparison of Intermolecular and Intramolecular Systems	204
Figure 9. Allylic Strain and Transannular Interaction in Pd-Amido Macrocyclic	215
Figure 10. Substrates Used in Stoichiometric Investigation	278
Figure 11. Catalysts Used in Stoichiometric Investigation	278
Figure 12. ^1H NMR Spectrum of V-6	303
Figure 13. ^1H NMR spectrum of V-7	304
Figure 14. ^1H NMR spectrum of V-8	305
Figure 15. ^1H NMR Spectrum of Oxidative Addition Complex V-9	306
Figure 16. ^1H NMR Spectrum of Oxidative Addition Complex V-10	307
Figure 17. ^1H NMR Spectrum of Oxidative Addition Complex V-11	308
Figure 18. ^1H NMR Spectrum of V-13	309
Figure 19. ^1H NMR spectrum of V-13b	310

Figure 20. ^1H NMR spectrum of V-14	311
Figure 21. ^1H NMR spectrum of V-15	312
Figure 22. ^1H NMR spectrum of V-16	313
Figure 23. $^1\text{H}, ^1\text{H}$ -NMR COSY of Oxidative Addition Complex V-9	314
Figure 24. ^1H NMR spectrum of V-12	315

LIST OF TABLES

Table 1. Carboamination of II-42 with 2-Br-Naphthalene: Optimization of Reaction	
Conditions.....	23
Table 2. Carboamination of II-42 with Aryl Bromides.....	24
Table 3. Carboamination of II-45, II-50 with Aryl and Vinyl Bromides.....	26
Table 4. Carboamination of II-33 with 4-Br- <i>t</i> Bu-benzene: Optimization of Reaction	
Conditions	27
Table 5. Carboamination of II-33 with 2-Br-Naphthalene: Optimization of Reaction	
Conditions.....	29
Table 6. Carboamination of II-33 with 2-Br-Naphthalene: Optimization of Phosphine:	
Metal Ratio.....	30
Table 7. Carboamination of II-33, II-49, II-54 with Aryl Halides	31
Table 8. Optimization of Carboamination of II-33 with 2-Br-Naphthalene using Cs ₂ CO ₃	
in Dioxane Solvent.....	33
Table 9. Optimization of Carboamination Reaction for Synthesis of 2,6-Disubstituted	
Piperazines	67
Table 10. Synthesis of 2,6-Disubstituted Piperazines.....	70
Table 11. Carboamination Reaction of δ -Amino Olefins with Vinyl Halides	72
Table 12. Carboamination Reaction of δ - <i>N</i> -Boc-Protected Amino Olefins with 4-Br-	
Benzonitrile.....	73
Table 13. Dependence of Diastereoselectivity on N1-Protecting Group.....	80

Table 14. N4-Protecting Group Diastereoselectivity Study	81
Table 15. Synthesis of Benzopiperazines	91
Table 16. Optimization of Carboetherification Reaction of IV-56	173
Table 17. Carboetherification Ligand Screen of IV-48	178
Table 18. Carboetherification Ligand Screen of IV-58	180
Table 19. Carboetherification Ligand Screen of IV-50	181
Table 20. Carboetherification Ligand Screen of IV-49	186
Table 21. Carboetherification Ligand Screen of IV-57	187
Table 22. Assignment of All Benzhydrylidene[1-(5-phenyltetrahydrofuran-2-yl)indan-5-yl] Stereoisomers (IV-83, IV-85, IV-83b, IV-85b)	190
Table 23. Optimization of Carboamination Reaction of IV-60	191
Table 24. Assignment of All <i>N</i> ,5-diphenyl-2-indan-1-ylpyrrolidine Stereoisomers (IV-104, IV-111, IV-112, IV-110).....	201

LIST OF ABBREVIATIONS

Ac	acetyl
Ar	generic aryl group
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
Bu	butyl
Bz	benzoate
Cbz	carbobenzyloxy
CDI	1,1'-carbonyldiimidazole
Cy	cyclohexyl
dba	<i>trans, trans</i> -dibenzylideneacetone
DCC	dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3 <i>H</i>)-one
DMA	<i>N,N</i> -dimethylacetamide
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DPE-phos	1,2 bis-(diphenylphosphino)diphenyl ether
dppb	1,2 bis-(diphenylphosphino)butane
dppe	1,2 bis-(diphenylphosphino)ethane

dppf	1,1'-bis-(diphenylphosphino)ferrocene
dppm	1,1 bis-(diphenylphosphino)methane
fur	furyl
HMPA	hexamethylphosphoramide
HOBT	hydroxybenzotriazole
KHMDS	potassium bis(trimethylsilyl)amide
L	general neutral ligand
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
MeCN	acetonitrile
MOM	methoxymethyl
Ph	phenyl
PG	protecting group
PMP	<i>para</i> -methoxyphenyl
<i>i</i> -Pr	isopropyl
rt	room temperature
TBS	Di- <i>tert</i> -butylmethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl

TMS	trimethylsilyl
<i>o</i> -tol	3-methylphenyl
<i>p</i> -tol	4-methylphenyl
Ts	4-methylbenzenesulfonyl
X	general anionic ligand
Xantphos	9,9-dimethyl-bis-4,5-diphenylphosphinoxanthene

ABSTRACT

Investigation of the Pd-catalyzed carboamination reaction for the synthesis of substituted piperidines from δ -amino olefins and piperazine heterocycles from amino acid derivatives is described. These reactions are believed to proceed via an unprecedented insertion into a Pd–N bond of the key Pd-amido species. These reactions also proceed with excellent levels of 2,6-diastereocontrol (in many cases, >20:1 dr has been observed). The diastereoselectivity of these reactions is also dependent on the protecting group on the cyclizing nitrogen, where more electron rich aryl protecting groups provide more of the *cis*-diastereomer, whereas less electron rich protecting groups provide slightly lower diastereoselectivity, still favoring the *cis*-diastereomer. Our stereochemical model differs from related pyrrolidine cyclizations which also provide the *cis*-diastereomer. We hypothesized that the nitrogen is pyramidalized in the transition state leading to the piperazine and therefore the α -substituent can lie in the pseudoequatorial orientation. This hypothesis was tested by varying the protecting group on the cyclizing nitrogen to determine whether we could vary the diastereoselectivity by varying the degree of pyramidalization in the transition state. In addition to 2,6-disubstituted aryl-protected piperazines, we also extended the methodology to include vinyl-halide coupling partners (in addition to aryl halide coupling partners), Boc-protected piperazines, 2,3-disubstituted piperazines, bicyclic piperazines, and benzopiperazines.

The second part of this thesis details intramolecular Pd-catalyzed carboetherification and carboamination reactions for the synthesis of 2-indanyl tetrahydrofurans and 2-indanyl pyrrolidines. These reactions are believed to proceed through an unprecedented macrocyclic insertion into a Pd–O or Pd–N bond to afford products resulting from syn-addition across the olefin. Surprisingly, in the optimization of the carboetherification reactions, we discovered an unprecedented catalyst control on the stereochemical outcome of the reaction. In cases where a monodentate ligand was used in combination with a Pd(0) source, we observed selective formation of the syn-addition diastereomer. When we switched to a catalyst system composed of Pd(0) and a bidentate ligand, we observed formation of the anti-addition diastereomer. We reasoned we were observing a catalyst control of mechanism in the oxypalladation reaction. In the analogous carboamination reactions, we did not observe a complete reversal of diastereoselectivity, but instead erosion of diastereoselectivity. We reasoned this was due to several factors, including the reduced pKa of the aniline versus the alcohol. Further studies to expand the scope of the intramolecular carboetherification and carboamination were also demonstrated.

Part One

Pd-Catalyzed Carboamination Reactions: Synthesis of Piperidines and Piperazines

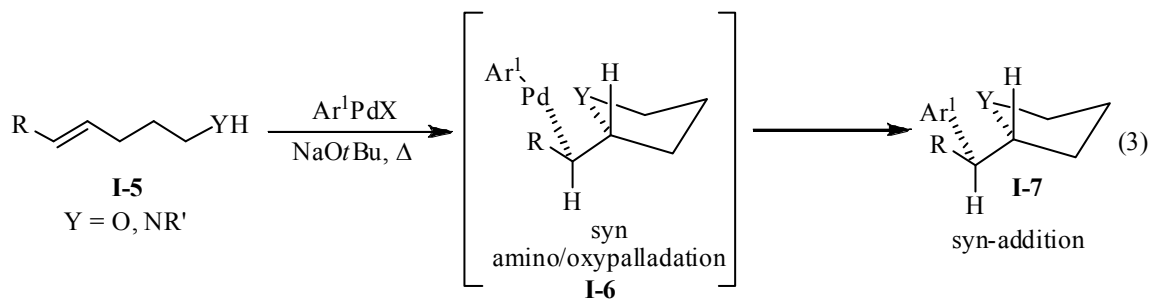
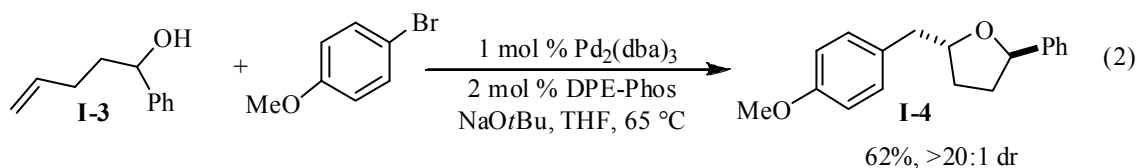
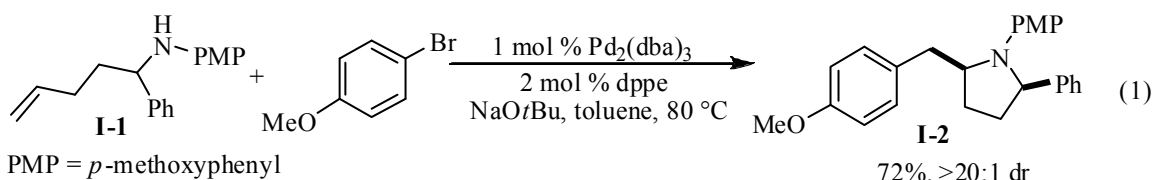
Chapter I

Synthesis of Pyrrolidines and Tetrahydrofurans via Pd-Catalyzed Carboamination and Carboetherification Reactions of γ -Hydroxy and γ -Amino Alkenes with Aryl and Alkenyl Bromides

Our lab has recently reported the stereoselective synthesis of both pyrrolidines and tetrahydrofurans from γ -amino and γ -hydroxy olefins, respectively.¹ These Pd-catalyzed carboamination and carboetherification reactions involve the coupling of an aryl or alkenyl halide with a γ -hydroxy or γ -amino alkene in the presence of catalytic amounts of Pd₂(dba)₃ or Pd(OAc)₂ and a phosphine ligand. These reactions are extremely useful, as they provide heterocyclic scaffolds that are ubiquitous in nature and are found in many biologically active natural products and pharmaceuticals.^{2,3,4} In addition, these transformations form two new bonds and one stereocenter in a single operation. The carboamination and carboetherification reactions are particularly appealing in that they provide the heterocyclic product in one step from easily accessible starting materials and allow for the facile construction of analogs.

Two representative examples of these reactions are shown below (eq 1 and eq 2).

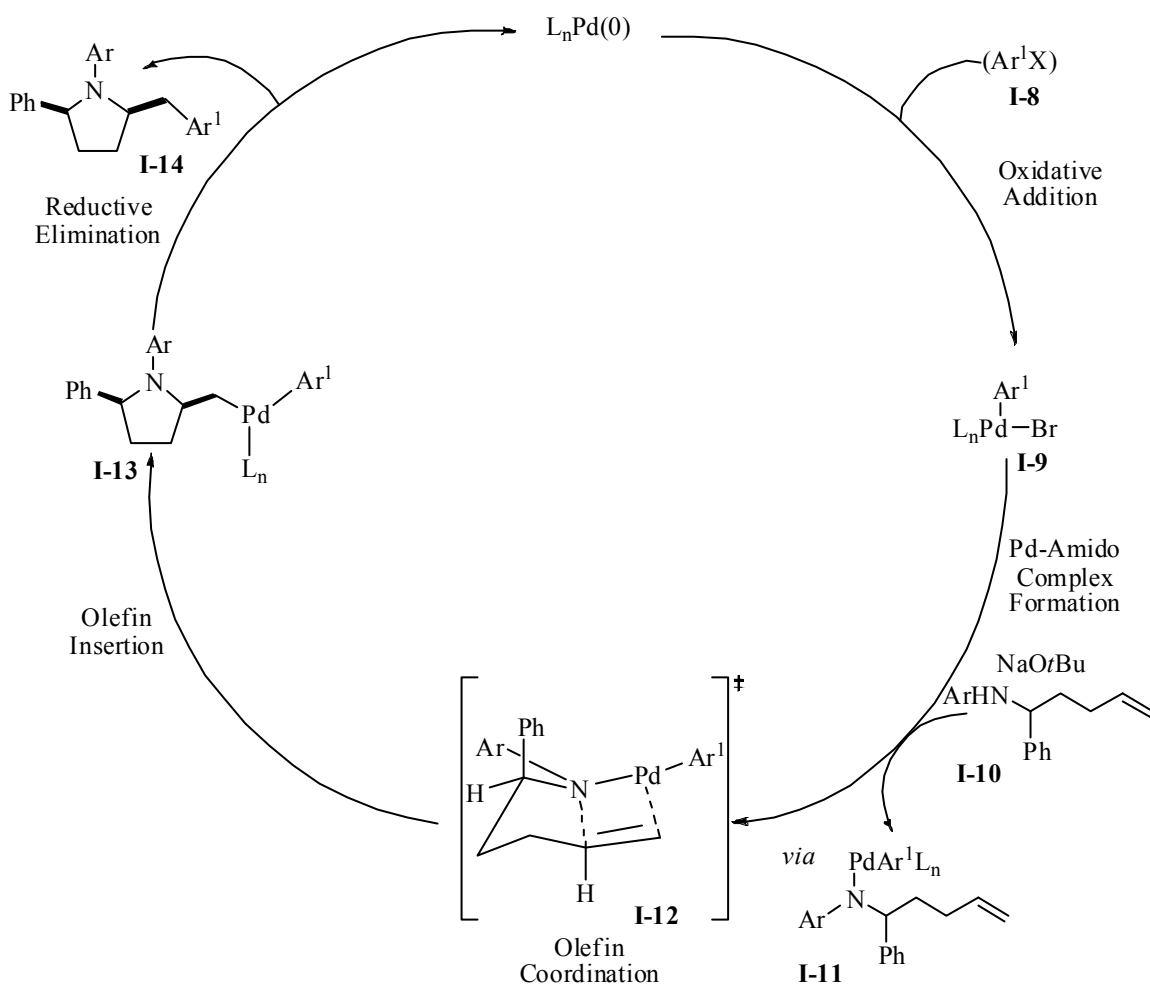
The carboamination of γ -amino olefin **I-1** with 4-bromoanisole proceeds with high diastereoselectivity for formation of 2,5-*cis*-disubstituted pyrrolidine **I-2**, whereas the analogous carboetherification of γ -hydroxy olefin **I-3** proceeds with high diastereoselectivity for the generation of 2,5-*trans*-disubstituted tetrahydrofuran **I-4**. These transformations are effective with a broad range of aryl or alkenyl halides, and have all been used for the stereoselective synthesis of 2,3-*trans*-disubstituted products. Both cyclic and acyclic internal alkenes (**I-5**) react with net syn-addition across the alkene (eq 3).¹



Both the carboamination and the carboetherification reaction proceed through a similar mechanism. The proposed catalytic cycle for the Pd-catalyzed carboamination

reaction is shown in Scheme 1. Oxidative addition of an aryl halide (**I-8**) to Pd(0) affords the electrophilic Pd(II) species **I-9**. The amine moiety of **I-10** coordinates to the metal, and is subsequently deprotonated to afford Pd-amido species **I-11**.⁵ Coordination of the olefin to the metal followed by insertion of the olefin into the Pd–N bond^{6,7} by way of transition state **I-12**, provides Pd(II)-pyrrolidine species **I-13**. Reductive elimination of **I-13** releases the pyrrolidine product **I-14**.

Scheme 1. Proposed Catalytic Cycle for Pd-Catalyzed Carboamination Reaction

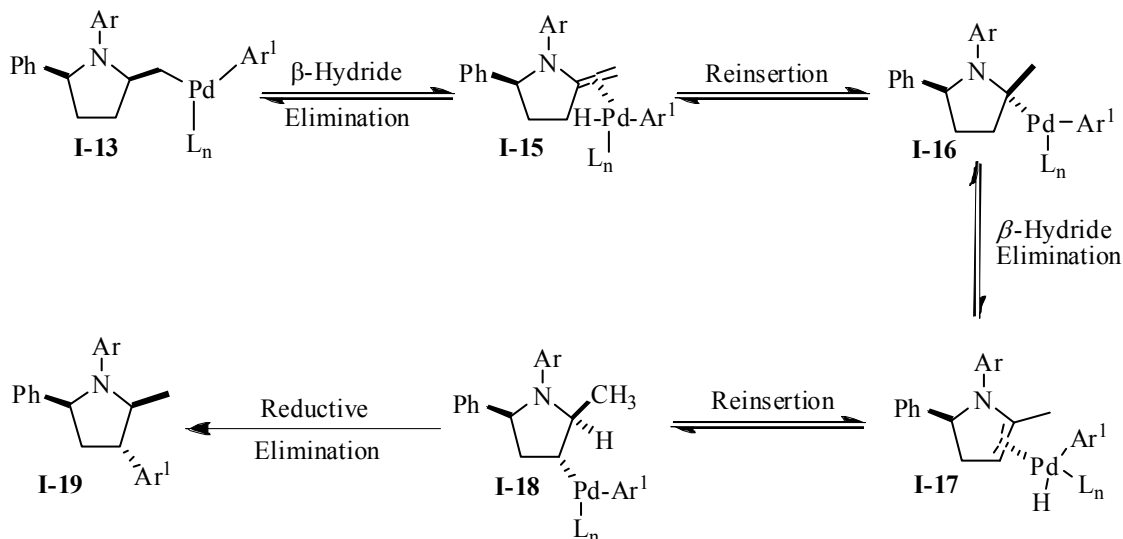


While the yields of the pyrrolidine products are generally quite good, competing processes have been observed as shown in Scheme 2.^{1a} In addition to the desired

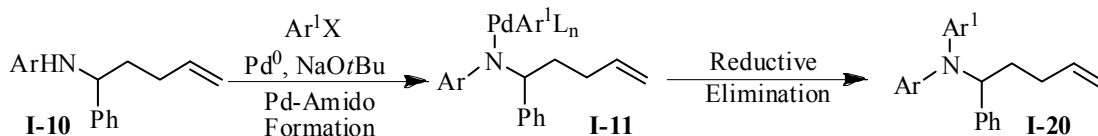
pyrrolidine **I-14**, a regioisomer is also generated (**I-19**). Additionally, *N*-arylation (**I-20**) of the substrate occasionally competes with the desired carboamination reaction. The origin of the regioisomer as well as the *N*-arylation side product can be easily explained when considering the mechanism. Regioisomer formation presumably originates from β -hydride elimination of intermediate **I-13** to afford **I-15**. At this stage, reinsertion of the olefin into the Pd–H bond with the opposite regiochemistry provides **I-16**. β -Hydride elimination from **I-16** affords **I-17**, which upon reinsertion generates **I-18**. Reductive elimination from **I-18** provides regioisomer **I-19**. This competing side reaction is minimized when the nitrogen is substituted with a *tert*-butoxycarbonyl or acyl protecting group in place of an aryl group.^{1c} The *N*-arylation side product likely derives from reductive elimination of Pd-amido species **I-11** and can be minimized by use of electron withdrawing *N*-substituents.

Scheme 2. Origin of Side Products in Pd-Catalyzed Carboamination Reactions

Origin of Regioisomeric Side Product I-19



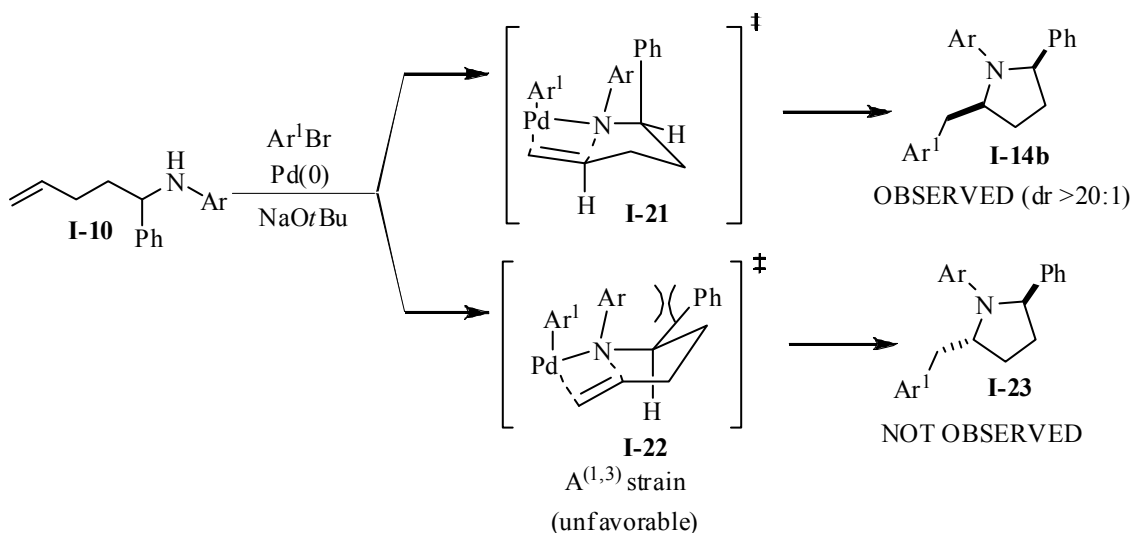
Origin of *N*-Arylation Side Product I-20



The current stereochemical model for the carboamination of γ -amino olefins **I-10** to provide 2,5-*cis*-disubstituted pyrrolidines **I-14** (or enantiomer **I-14b**) is explained by an allylic-strain based stereochemical hypothesis (Scheme 3). In these cyclizations two transition states are possible, one placing the α -substituent in the pseudoaxial orientation as in **I-21**, and the other placing the α -substituent in the pseudoequatorial position as in **I-22**. Transition state **I-22** is likely disfavored because of the $A^{(1,3)}$ strain that develops between the aryl substituents and the pseudoequatorial substituent, and therefore the α -substituent prefers to orient itself in the pseudoaxial position. Upon insertion and subsequent reductive elimination, 2,5-*cis*-pyrrolidine **I-14b** is generated. The same

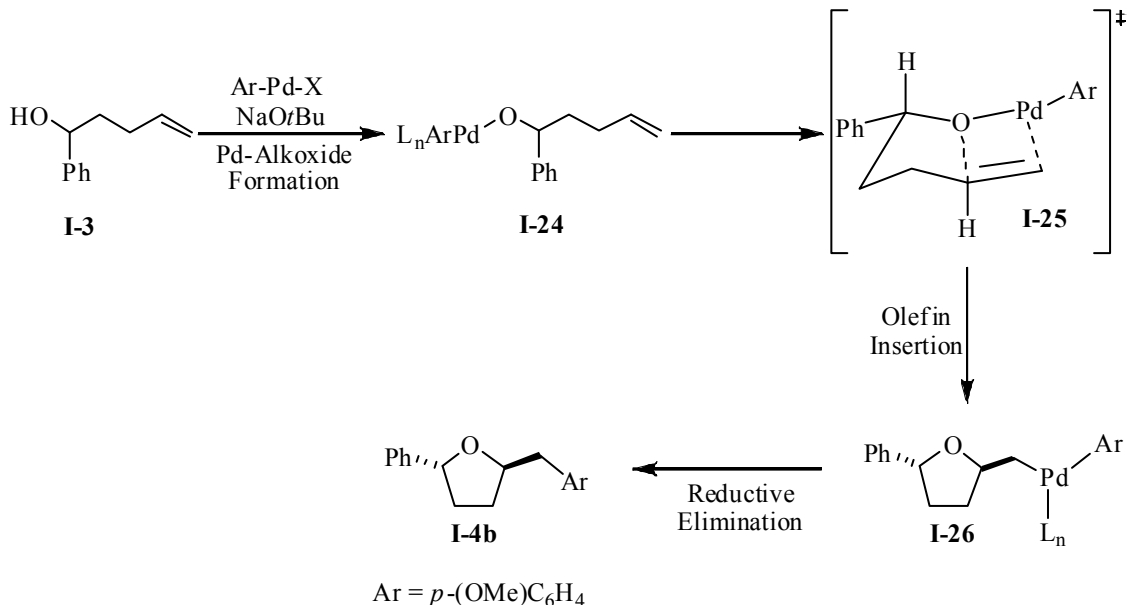
argument is used in the explanation of the stereochemistry in the *N*-Boc pyrrolidine series.^{1a-c}

Scheme 3. Stereochemical Model for Pd-Catalyzed Intermolecular Carboamination Reactions



The Pd-catalyzed carboetherification reaction is believed to proceed through a similar mechanism as the pyrrolidine-forming reactions described above.^{1d-g} However, the conversion of **I-3** to **I-4** (or enantiomer **I-4b**) is believed to proceed through a transition state in which the α -substituent orients itself in the pseudoequatorial position (**I-25** in Scheme 4). Since there is not an allylic strain component in this transformation, the 2,5-*trans*-disubstituted tetrahydrofuran is generated upon insertion and reductive elimination.

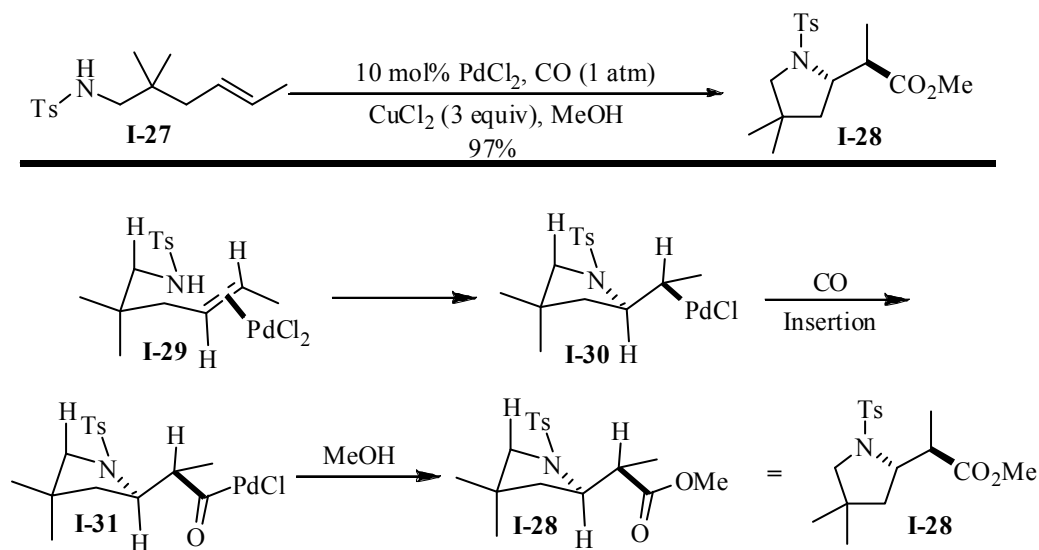
Scheme 4. Mechanism of Pd-Catalyzed Intermolecular Carboetherification Reaction



Other Pd-Catalyzed Carboamination and Carboetherification Reactions

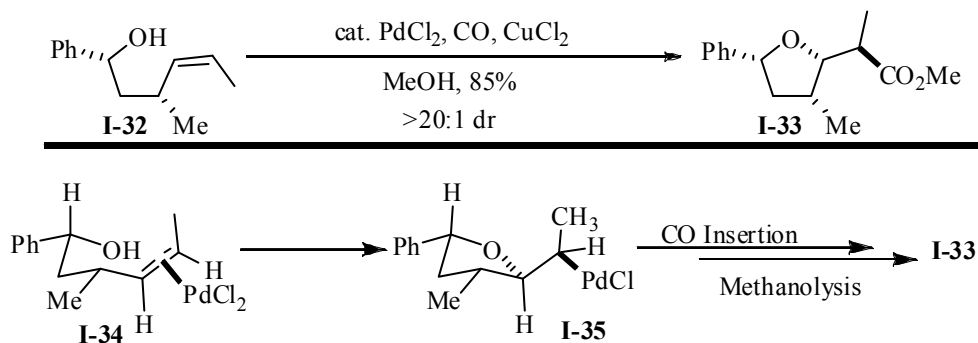
Three groups have also reported metal-catalyzed carboamination reactions for the synthesis of pyrrolidines or tetrahydrofurans. Tamaru⁸ has shown that *N*-tosyl protected alkene substrate **I-27** cyclized to afford pyrrolidine **I-28**, with the reaction proceeding through a nucleophilic attack of the heteroatom onto the Pd-activated olefin as shown in the conversion of **I-29** to **I-30** (Scheme 5). Upon nucleophilic attack and loss of HCl, insertion of CO occurs into the Pd–C bond to afford **I-31**, which upon methanolysis affords pyrrolidine **I-28**. It is important to note that the heteroatom and the metal add anti across the olefin, which has important consequences with regard to the mechanism of the reaction. This type of carboamination is mechanistically distinct from those discussed in the previous section, which have been shown to proceed by syn-addition across the double bond.^{1a-c} This reaction is very useful for the synthesis of pyrrolidines but is limited to the preparation of molecules bearing an ester group in the C1' position.⁹

Scheme 5. Mechanism of Pd-Catalyzed Anti-Aminocarbonylation Reaction



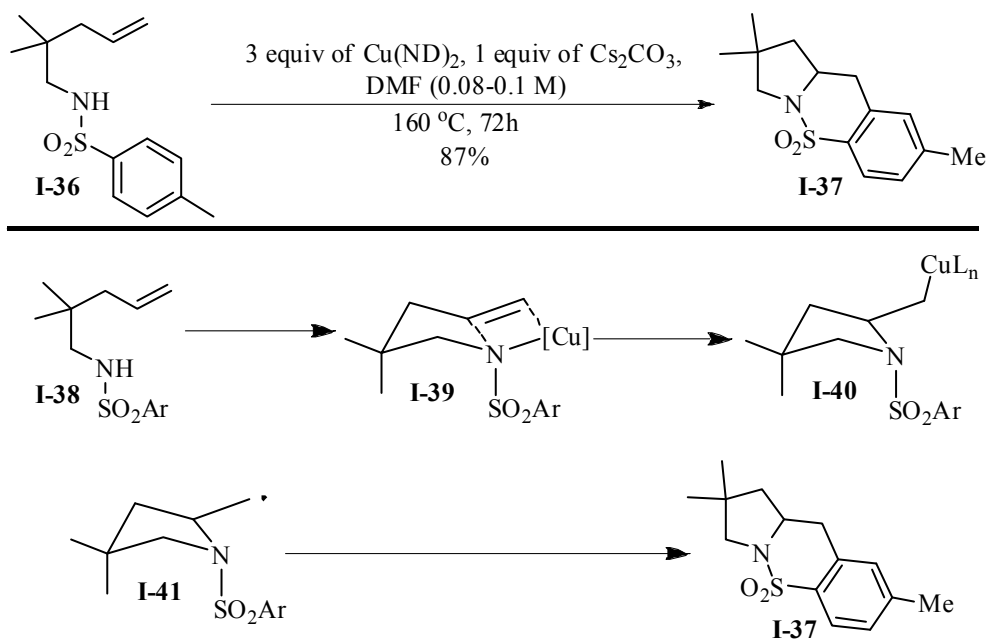
In related cyclizations for the synthesis of tetrahydrofurans, Semmelhack has demonstrated the conversion of **I-32** to tetrahydrofuran **I-33** under an atmosphere of CO (Scheme 6). This reaction proceeds via anti-oxypalladation to provide **I-35**, and is mechanistically analogous to the Tamaru reaction discussed in Scheme 5.^{10,11}

Scheme 6. Mechanism of Pd-Catalyzed Anti-Oxycarbonylation Reaction



Chemler¹² has recently demonstrated the synthesis of pyrrolidines through an intramolecular carboamination reaction that is proposed to proceed through a copper(II)–amido species. While this method is mechanistically distinct from the anti-aminopalladation pathway of the Tamaru reactions, it is limited in substrate scope; the aryl moiety must be tethered to the substrate via a sulfonamide linkage. The mechanism as proposed by Chemler involves formation of Cu-amido complex **I-39** followed by migratory insertion to form the copper alkyl species **I-40**. Formation of intermediate **I-41** occurs through Cu–C bond homolysis, which is followed by radical cyclization onto the aromatic ring to generate the product **I-37** (Scheme 7).

Scheme 7. Intramolecular Cu-Mediated Carboamination Reactions Providing Syn-Addition Products



The Pd-catalyzed carboamination and carboetherification reactions developed in our research group are mechanistically distinct and complementary to other metal-

catalyzed methods for the synthesis of heterocycles because of substitution pattern, scope of coupling partners, and stereochemistry of insertion. In addition, the reactions are highly efficient and exemplary as evidenced by the excellent yields, regioselectivity, and diastereoselectivity observed. However, the Pd-catalyzed carboamination and carboetherification reactions developed by our research group have not been previously employed for the preparation of six-membered ring heterocycles. In addition, an intramolecular version of the reaction, which would ultimately form two bonds, two rings, and two contiguous stereocenters in one step has also not been shown. The first part of this thesis describes our effort in the development of the carboamination reaction for the synthesis of six-membered ring heterocycles. The second part of this thesis describes the development of the intramolecular Pd-catalyzed carboamination and carboetherification reaction for the synthesis of 2-indan-1-ylpyrrolidines and 2-indan-1-yltetrahydrofurans from aryl bromides with tethered unsaturated amines and alcohols, respectively.

References

¹ (a) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605–3608. (b) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906–13907. (c) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447–6459. (d) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644–8651. (e) Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575–2578. (f) Ney, J. E.; Hay, M. B.; Yang, Q.; Wolfe, J. P. *Adv. Synth. Catal.* **2005**, *347*, 1614–1620. (g) Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353–2356. (h) Dongol, K. G.; Tay, B. Y. *Tetrahedron Lett.* **2006**, *47*, 927–930. (i) Bertrand, M. B.; Leathen, M. L.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 457–460. (j) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571–582. (k) Peng, J.; Lin, W.; Yuan, S.; Chen, Y. *J. Org. Chem.* **2007**, *72*, 3145–3148.

²For reviews see: Pyrrolidines: (a) Massiot, G.; Delaude, C. *Alkaloids* **1986**, *27*, 269–322. (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446. (c) Mitchinson, A.; Nadi A. *J. Chem. Soc., Perkin Trans. I* **2000**, 2862–2892. (d) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773–781. (e) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625–649. Tetrahydrofurans: (f) Hou, X.-L.; Yang, Z.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2002**, *14*, 139–179.

³ (a) Schwartz, R. E.; Liesch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A.; Onishi, J.; Monaghan, R. *J. Antibiot.* **1988**, *41*, 1774–1779. (b) Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, *42*, 1184–1185. (c) Kasahara, K.; Yoshida, M.; Eishima, J.; Takesako, K.; Beppu, T.; Horinouchi, S. *J. Antibiot.* **1997**, *50*, 267–269. (d) Achenbach, T. V.; Slater, E. P.; Brummerhop, H.; Bach, T.; Müller, R. *Antimicrob. Agents Chemother.* **2000**, *44*, 2794–2801. (e) Kinzy, T. G.; Harger, J. W.; Carr-Schmid, A.; Kwon, J.; Shastry, M.; Justice, M.; Dinman, J. D. *Virology* **2002**, *300*, 60–70. (f) Sobin, B. A.; Tanner, F. W., Jr. *J. Am. Chem. Soc.* **1954**, *76*, 4053. (g) Hall, S. S.; Loebenberg, D.; Schumacher, D. P. *J. Med. Chem.* **1983**, *26*, 469–475. (h) Schwaradt, O.; Veith, U.; Gaspard, C.; Jäger, V. *Synthesis* **1999**, 1473–1490. (i) Shibano, M.; Kitagawa, S.; Kusano, G. *Chem. Pharm. Bull.* **1997**, *45*, 505–508. (j) Shibano, M.; Kitagawa, S.; Nakamura, S.; Akazawa, N.; Kusano, G. *Chem. Pharm. Bull.* **1997**, *45*, 700–705. (k) Shibano, M.; Nakamura, S.; Akazawa, N.; Kusano, G. *Chem. Pharm. Bull.* **1998**, *46*, 1048–1050. (l) Shibano, M.; Nakamura, S.; Kubori, M.; Minoura, K.; Kusano, G. *Chem. Pharm. Bull.* **1998**, *46*, 1416–1420. (m) Shibano, M.; Tsukamoto, D.; Fujimoto, R.; Masui, Y.; Sugimoto, H.; Kusano, G. *Chem. Pharm. Bull.* **2000**, *48*, 1281–1285.

⁴ (a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L.; *J. Nat. Prod.* **1999**, *62*, 504–540. (b) Figadere, B. *Acc. Chem. Res.* **1995**, *28*, 359–365. (c) Zafra-Polo, M. C.; Figadere, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087–1117. (d) For isolation, see: Alkofahi, A.; Rupprecht, J. K.; Liu, Y. M.; Chang, C. J.; Smith, D. L.; McLaughlin, J. L. *Experientia* **1990**, *46*, 539–541.

⁵ (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209. (b) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067. (c) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417–1423.

⁶ Insertion of an olefin into a Pd–N bond has not been observed. For insertion of activated alkynes into Pd–N bonds, see: (a) Villanueva, L. A.; Abboud, K. A.; Boncella, J. M. *Organometallics* **1992**, *11*, 2963–2965. (b) VanderLende, D. D.; Abboud, K. A.; Boncella, J. M. *Inorg. Chem.* **1995**, *34*, 5319–5326. (c) Dahlenburg, L.; Herbst, K. *J. Chem. Soc., Dalton Trans.* **1999**, 3935–3939.

⁷ Insertion of an activated olefin into a Pt–N bond has been observed, see: (a) Cowan, R. L.; Trogler, W. C. *Organometallics* **1987**, *6*, 2451–2453. (b) Cowan, R. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4750–4761.

⁸ (a) Tamaru, Y.; Kobayashi, T.; Kawamura, S.-i.; Ochiai, H.; Yoshida, Z.-i. *Tetrahedron Lett.* **1985**, *26*, 4479–4482. (b) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z.-i. *J. Am. Chem. Soc.* **1988**, *110*, 3994–4002. (c) Tamaru, Y.; Hojo, M.; Yoshida, Z.-i. *J. Org. Chem.* **1988**, *53*, 5731–5741. (d) Harayama, H.; Okuno, H.; Takahashi, Y.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1996**, *37*, 7287–7290. (e) Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1997**, *62*, 2113–2122.

⁹ For reviews describing carboamination reactions proceeding via anti-addition see: (a) Tamaru, Y.; Yoshida, Z.-i. *J. Organomet. Chem.* **1987**, *334*, 213–223. (b) Tamaru, Y.; Kimura, M. *Synlett* **1997**, 749–757.

¹⁰ Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496–1498.

¹¹ (a) Semmelhack, M. F.; Zhang, N. *J. Org. Chem.* **1989**, *54*, 4483–4485. (b) Semmelhack, M. F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure. Appl. Chem.* **1990**, *62*, 2035–2040. (c) Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, *30*, 4925–4928. (d) Semmelhack, M. F.; Epa, W. R. *Tetrahedron Lett.* **1993**, *34*, 7205–7208.

¹² Sherman, E. S.; Fuller, P. H.; Kasi, D.; Chemler, S. R. *J. Org. Chem.* **2007**, *72*, 3896–3905.

Chapter II

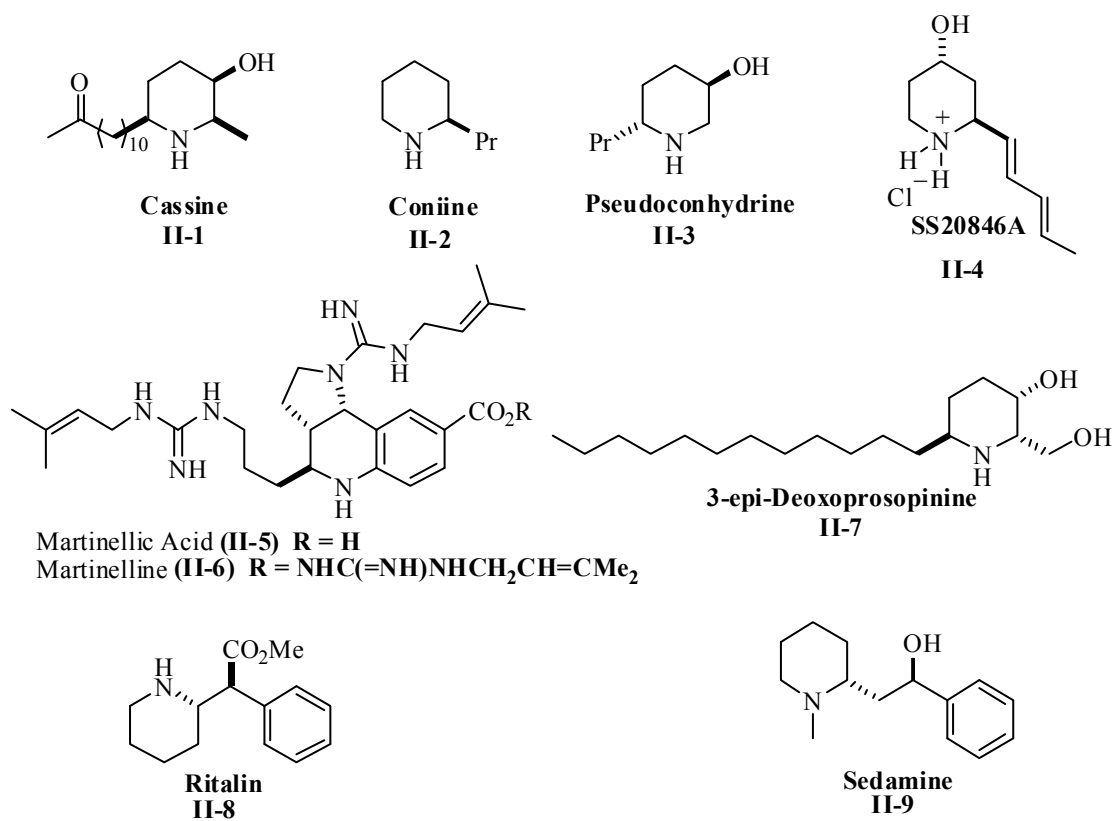
Carboamination Reactions for the Synthesis of Piperidines¹

Introduction: Biologically Active Piperidine Natural Products and Pharmaceuticals

The piperidine core is an incredibly important motif contained in a wide variety of natural products as shown below.² Cassine (**II-1**)^{3,4,5} is an alkaloid isolated from the American tropical legume *Cassia excelsa* Shrad and exhibits antimicrobial activity against *Staphylococcus aureus*. Additionally, other 2,6-disubstituted piperidin-3-ol alkaloids display biological activities, such as prosopinine (analgesic, anesthetic, and antibiotic activities) and (–)-spectaline (cytotoxic activities). Coniine (**II-2**) and pseudoconhydrine (**II-3**)^{6,7} are both poisonous alkaloids from the hemlock (*Conium maculatum*). Coniine (**II-2**) is one of the most toxic of these alkaloids, and is well known for possibly claiming the life of Socrates.^{2e} Sedamine (**II-9**)⁸ is a piperidine derivative that is one of over 600 alkaloids isolated from the species *Sedum*, which is a common garden plant. Methylphenidate, marketed under the trade name Ritalin (**II-8**),⁹ is a well known drug used to treat attention deficit disorder. Martinelic acid (**II-5**) and martinelline (**II-6**) originate from the root extracts of the *Martinella iquitosensis* vine, found in the Amazonian lowland rainforests. These root extracts are used by indigenous tribes to treat eye ailments such as inflammation and conjunctivitis, and this positive effect is believed to be at least partially due to the guanidine moiety.¹⁰ Alkaloids **II-5** and **II-6** have been found to be antibiotics and G-protein coupled receptor antagonists.¹¹ The

2-alkyl-4-hydroxypiperidine SS20846A (**II-4**) was isolated from *Streptomyces* sp S20846 and exhibits antibacterial and anticonvulsant properties.¹² The *Prosopis* family of natural products, of which the natural product 3-*epi*-deoxoprosopinine (**II-7**) is a member, exhibit various bioactivities including analgesic, anesthetic, and antibiotic activity.^{2e}

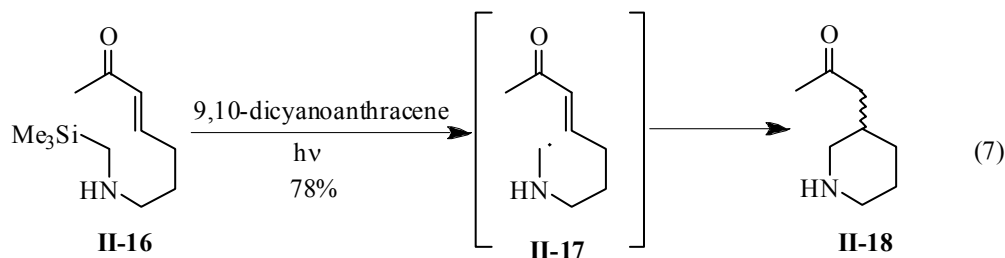
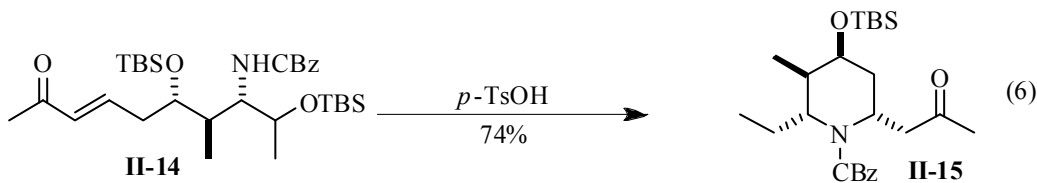
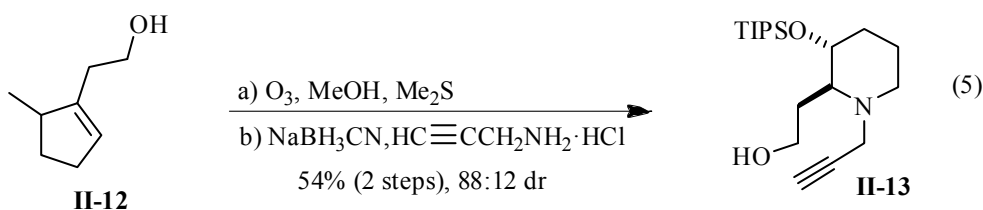
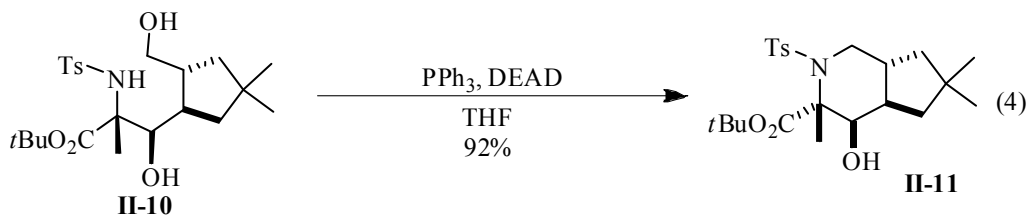
Figure 1. Biologically Active Piperidine Natural Products and Pharmaceuticals



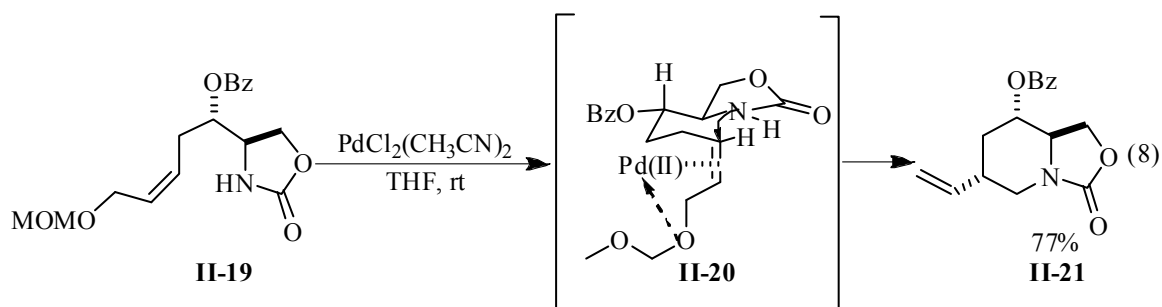
Background: Classical and Pd-catalyzed Methods for the Synthesis of Piperidines

There are numerous methods for the stereoselective synthesis of piperidines.² The most commonly used strategies involve reactions of amines with tethered alkyl halides, acetates, mesylates, and alcohols under Mitsunobu conditions (eq 4).¹³ Reductive

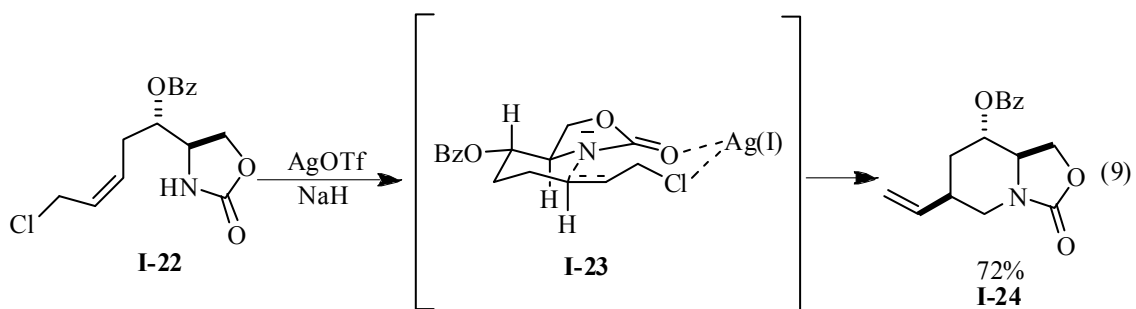
aminations (eq 5),¹⁴ Michael additions (eq 6),¹⁵ and radical cyclizations (eq 7) are also commonly employed methods to generate the piperidine core.¹⁶



Metal-catalyzed methods have also been developed and a few examples are highlighted below. Hirai¹⁷ reported the stereoselective synthesis of vinyl piperidine **II-21** from oxazolidinone **II-19** in the presence of a Pd-catalyst. Activation of the alkene by Pd(II) followed by nucleophilic attack occurs via transition state **II-20** to afford **II-21** after β -alkoxide elimination.



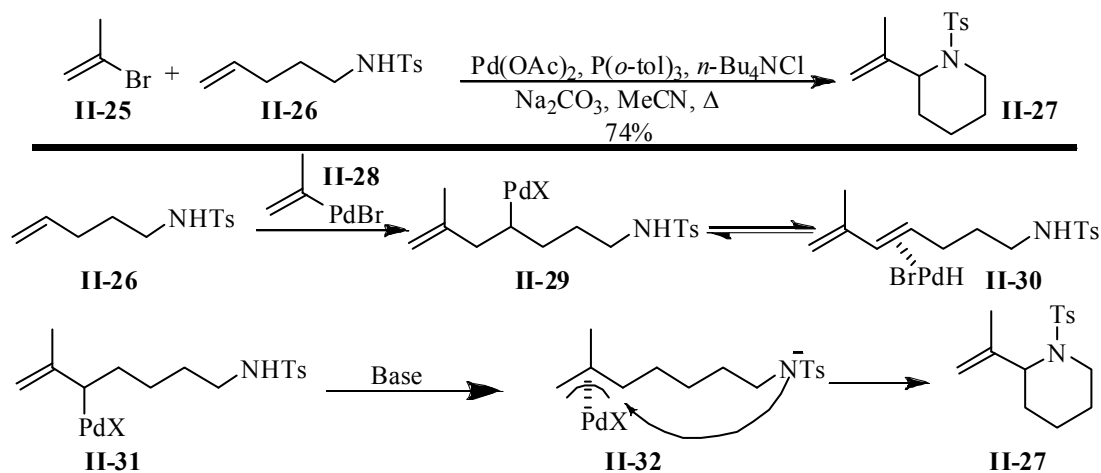
Interestingly, use of AgOTf as the catalyst with added NaH as base leads to the conversion of related substrate **I-22** to **I-24**. This reversal of diastereoselectivity is presumably due to the differences in coordination properties of the two metals, which consequently results in a difference in transition state leading to the piperidine products. When AgOTf is used as the catalyst, both the chloride atom and carbonyl oxygen of the substrate bind to the catalyst, and an S_N2' reaction ensues via transition state **I-23**, which leads to the formation of **I-24**.



Larock, Weinreb and coworkers¹⁸ reported the synthesis of vinyl piperidines such as **II-27** from *N*-tosyl amino olefins (e.g. **II-26**) and vinyl halides (**II-25**) in the presence of a Pd-catalyst. Carbopalladation of **II-26** with the (alkenyl)Pd(Br) intermediate (generated from oxidative addition of **II-25** to Pd(0)) affords **II-29**. This intermediate then undergoes β -hydride elimination and reinsertion to provide **II-30**. Nucleophilic

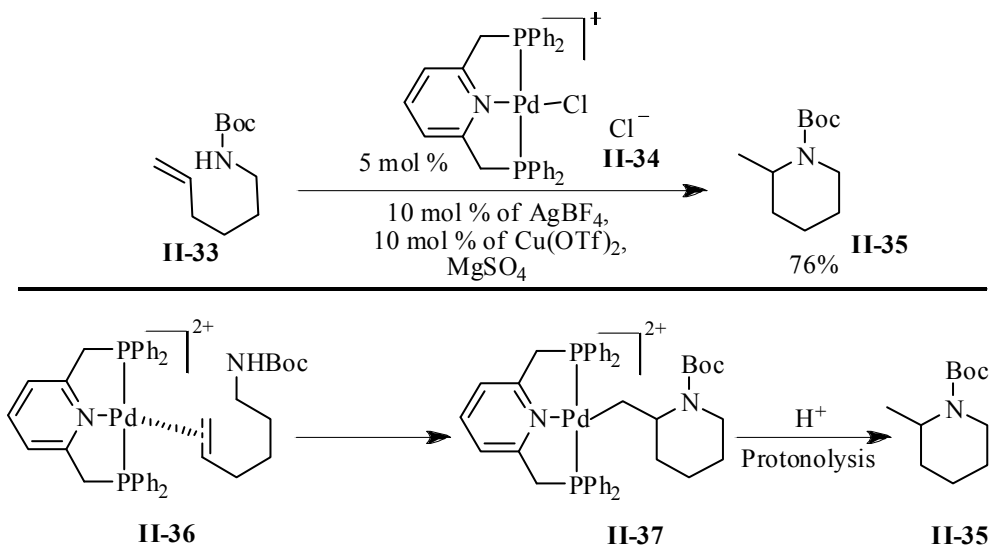
attack of the pendant sulfonamide on the π -allyl palladium intermediate, affords the piperidine product **II-27**.

Scheme 8. Carboamination Reactions for the Synthesis of 2-Vinyl Piperidines



Michael and coworkers recently reported a hydroamination reaction of amino olefin substrates to provide piperidines.¹⁹ For example, amino olefin **II-33** was converted to methyl substituted piperidine **II-35** in the presence of the tridentate Pd-catalyst **II-34** and AgBF_4 . These reactions presumably proceed through nucleophilic attack of the amine on the Pd-activated olefin. Upon protonolysis, the product piperidine is generated (**II-35**).

Scheme 9. Hydroamination Reactions for the Synthesis of Piperidines

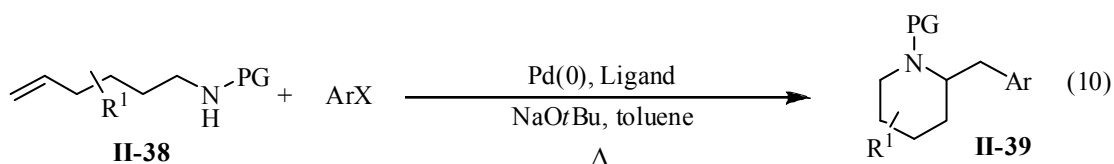


Pd-Catalyzed Carboamination of δ -Amino Alkenes with Aryl Bromides

As noted in Chapter I, the generation of six-membered rings through Pd-catalyzed carboamination or carboetherification reactions between heteroatom-tethered alkenes and aryl/alkenyl halides has not been previously described. We believed that we could apply the Pd-catalyzed carboamination reaction developed in our lab to the synthesis of larger rings. A logical extension from the pyrrolidine synthesis would be to simply insert a methylene group in the tether to afford the six-membered ring analog (piperidine). With this in mind, we set out to examine the analogous Pd-catalyzed carboamination reactions for the synthesis of six membered nitrogen heterocycles. In our initial studies, we chose to examine the carboamination reactions for the preparation of *N*-aryl piperidines.

Our goals for the synthesis of piperidines via Pd-catalyzed carboamination reactions were: 1) examine and identify suitable reaction conditions for the transformation of **II-38** to **II-39** (eq 10) by screening various ligands, which have been

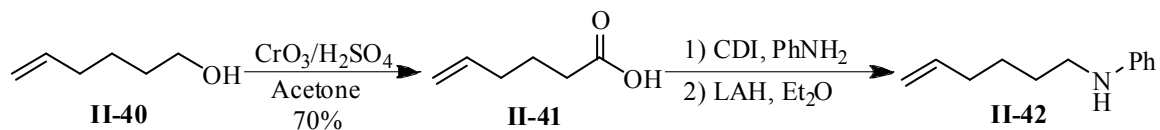
shown to have the largest impact on the chemical yield of the analogous five-membered ring transformations; and 2) examine the diastereoselectivity of reactions involving substituted δ -amino alkenes, which would provide disubstituted piperidines.



Substrate Synthesis

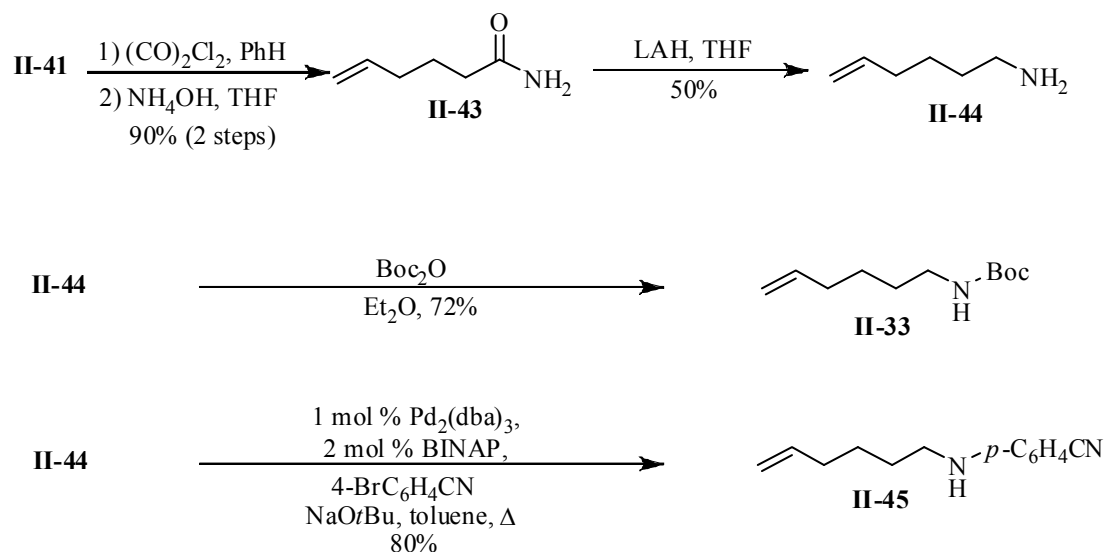
The substrates for these reactions were prepared in 3–5 steps from commercially available materials. Hydroxy olefin **II-40** was oxidized in the presence of the Jones reagent to provide carboxylic acid **II-41**. Treatment of carboxylic acid **II-41** with CDI followed by aniline provides an intermediate *N*-phenyl amide, which was reduced with lithium aluminum hydride to provide substrate **II-42**.²⁰

Scheme 10. Synthesis of δ -(*N*-Phenylamino) Alkenes



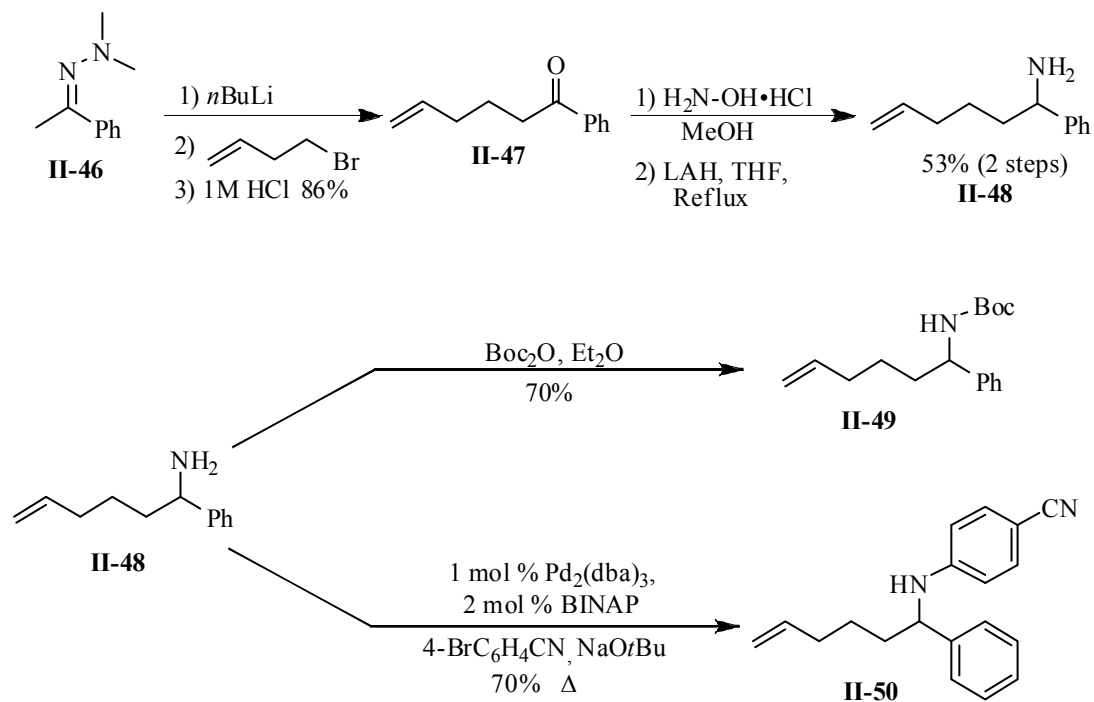
Alternatively, carboxylic acid **II-41** was treated with oxalyl chloride followed by NH_4OH to provide primary amide **II-43**. The amide was further elaborated by lithium aluminum hydride reduction to the primary amine **II-44** followed by *N*-arylation of the primary amine to afford **II-45**. Boc protection of **II-44** generates Boc-protected amine substrate **II-33**.²¹

Scheme 11. Synthesis of δ -(*N*-Boc-amino) and δ -(*N*-*p*-Cyanophenyl-amino) Alkenes

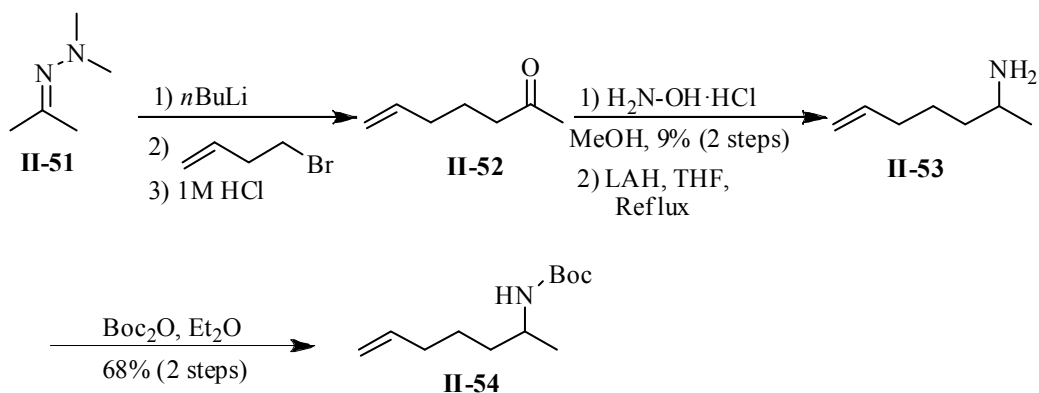


Substituted substrates were synthesized in 4 steps using the protocol shown in Schemes 12 and 13. Deprotonation of hydrazones **II-46** and **II-51** (formed in one step from acetophenone and acetone, respectively) followed by alkylation with 4-bromobutene affords ketones **II-47** and **II-52** after hydrolysis. Treatment of the ketone with hydroxylamine hydrochloride followed by lithium aluminum hydride reduction of the oxime affords primary amines **II-48** and **II-53**. Boc protection of **II-48** and **II-53** provides substrates **II-49** and **II-54**,²² or *N*-arylation of **II-48** provides substrate **II-50**.

Scheme 12. Synthesis of α -Phenyl-Substituted δ -(*N*-Boc-amino) and δ -(*N*-*p*-Cyanophenyl-amino) Alkenes



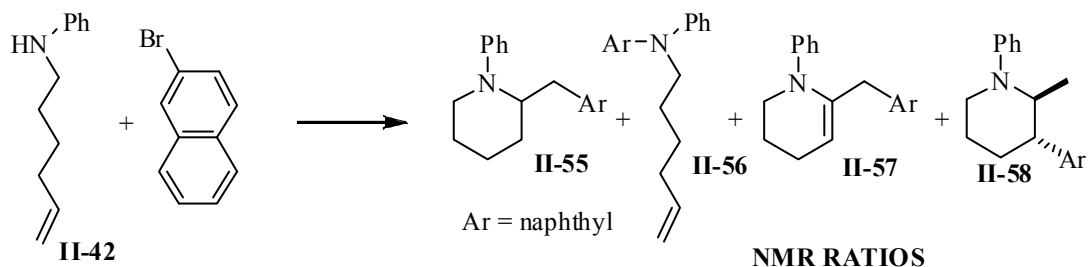
Scheme 13. Synthesis of α -Methyl-Substituted δ -(*N*-Boc-amino) Alkenes



Optimization of Pd-Catalyzed Carboamination Reaction for the Synthesis of Piperidines

With the substrates in hand, we set out to optimize the reaction as shown in Table 1.²³ Treatment of **II-42** with 2-bromonaphthalene and NaOtBu in the presence of catalytic Pd₂(dba)₃ and a phosphine ligand provided the piperidine product **II-55** as well as side products **II-56**, **II-57**, **II-58**. We found the best ligands for this reaction were P(2-fur)₃ and dppe, and use of 2.0 equiv of NaOtBu and ArBr provided optimal results. The use of P(2-fur)₃ was initially examined with a higher catalyst loading (Table 1), but use of other aryl halides determined that a higher catalyst loading was not necessary (Table 2).

Table 1. Carboamination of **II-42** with 2-Br-Naphthalene: Optimization of Reaction Conditions^a



LIGAND	% conversion	Piperidine (II-55) ^b	N-Arylation (II-56)	II-57 & II-58 ⁱ
dppm	100	33	16	51
PCy ₃ ·HBF ₄	67	22	11	34
P(2-fur)₃	98	86 (71^{c,d})	0	12
dppb ^e	34	23	10	0
dppb	87	57	17	13
dppe ^f	88	72	12	16
dppe ^g	100	62 (68 ^h)	0	38
dppe	100	82 (72^h)	0	18

^aConditions: 1.0 equiv **II-42**, 2.0 equiv ArBr, 2.0 equiv NaOtBu, 1 mol % Pd₂(dba)₃, 4 mol % monodentate ligand or 2 mol % bidentate ligand, toluene (0.2–0.5 M), 105 °C, 12h; reaction times have not been minimized. ^bThe yield in parentheses denotes the isolated yield. ^c2.5 mol % Pd₂(dba)₃, 10 mol % P(2-fur)₃ was used. ^dThe product was contaminated with ~5% of **II-57** + **II-58**. ^eThis reaction was conducted at 60 °C. ^f1 mol % Pd₂(dba)₃, 4 mol % dppe. ^g2 mol % Pd₂(dba)₃, 4 mol % dppe. ^hThe product was contaminated with ~10% of **II-57** + **II-58**. ⁱ**II-57** and **II-58** have been tentatively assigned as shown.

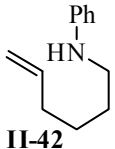
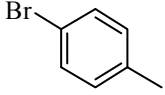
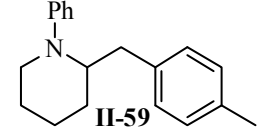
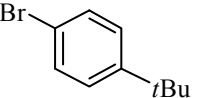
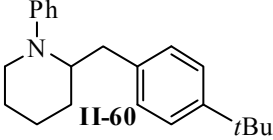
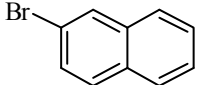
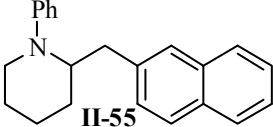
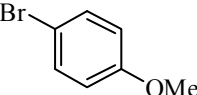
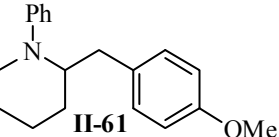
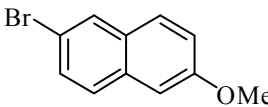
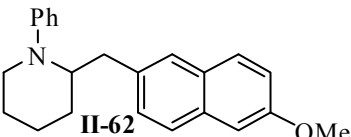
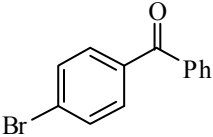
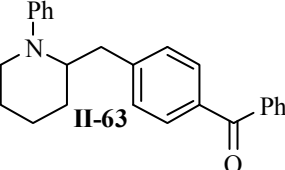
Scope and Limitations of Piperidine Synthesis via Pd-Catalyzed Carboamination

Reactions

With optimal conditions in hand, we set out to examine the scope of the carbamination reaction for the synthesis of piperidines. We initially examined reactions of the *N*-phenyl protected amino olefin **II-42** with various aryl halide coupling partners (Table 2). We were able to isolate piperidine products (entries 1-6) in good yield, but in some cases it was difficult to separate the desired products from the side products (analogous to **II-57** and **II-58** shown in Table 1). However, the products are generally

formed in moderate yields to good yields, and the reactions are effective with several different aryl bromides.

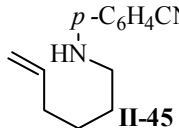
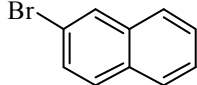
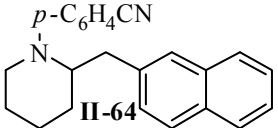
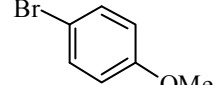
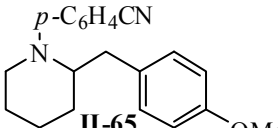
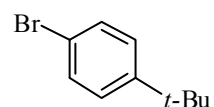
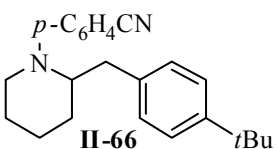
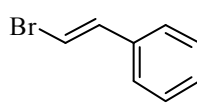
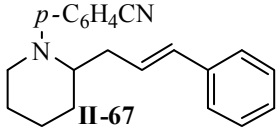
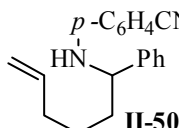
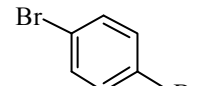
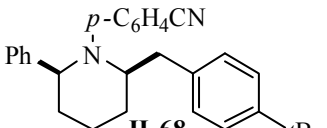
Table 2. Carboamination of **II-42** with Aryl Bromides^{a,e}

Entry	Amine Substrate	Aryl Bromide	Product	Yield
1				68%
2				80% ^b
3				72% ^{b,c}
4				63%
5				54%
6				56% ^d

^aConditions: 1.0 equiv **II-42**, 2.0 equiv ArBr, 2.0 equiv NaOtBu, 1 mol % Pd₂(dba)₃, 4 mol % P(2-fur)₃, toluene (0.2–0.5M), 105 °C, 12h; reaction times have not been minimized. ^bThe pure product was contaminated with ~10% of **II-57** + **II-58** for ArBr = 2-bromonaphthalene and **II-57b** + **II-58b** for ArBr = 4-Br-*t*Bu-benzene. ^c2 mol % dppe used in place of P(2-fur)₃. ^dThe pure product was contaminated with ~5% of *N*-arylation side product analogous to **II-56** but with ArBr = 4-bromobenzophenone (**II-56b**). ^eYields represent results of a single experiment.

We also examined the cyclization of the *N*-(*p*-cyanophenyl)-protected amino olefin **II-45** with various aryl halides (Table 3). The yields were comparable to those obtained in reactions of *N*-phenyl amino derivatives. Vinyl halides were briefly examined, and it was found that mono-substituted piperidines could be generated in moderate yield (Table 3, entry 4). Substituted substrates were also examined, and unfortunately, reaction of α -substituted amino olefins led to complex mixtures of products and low yields of the desired piperidine (entry 5). Reactions that proceeded in lower yields (Table 3, entries 4–5) were impeded by side products analogous to those discussed in the *N*-phenyl amine series (Table 2).

Table 3. Carboamination of **II-45**, **II-50** with Aryl and Vinyl Bromides^{a,b}

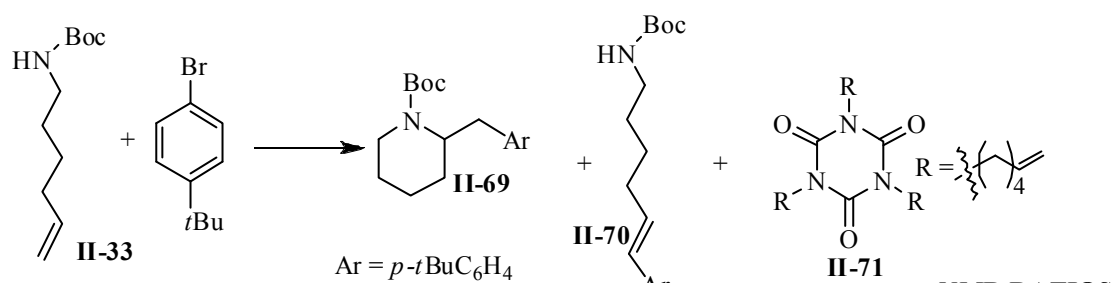
Entry	Amine Substrate	Aryl/Vinyl Bromide	Product	Yield
1	 II-45		 II-64	61%
2			 II-65	64%
3			 II-66	76% ^b
4			 II-67	49%
5	 II-50		 II-68	24% ^c 3-4:1 crude dr (5.7:1 dr isolated)

^aConditions: 1.0 equiv amine, 2.0 equiv ArBr, 2.0 equiv NaOtBu, 1 mol % Pd₂(dba)₃, 4 mol % P(2-furyl)₃ (entries 2, 4, and 5) or 2 mol % dppe (entries 1 and 3), toluene (0.2–0.5M), 105 °C, 12h; reaction times have not been minimized. ^bYields represent results of a single experiment, except entry 3 which is an average of two experiments. ^cThe assigned stereochemistry is tentative.

Previous studies on related pyrrolidine-forming carboamination reactions suggested that *N*-Boc-protected substrates might undergo cleaner cyclization.²⁴ Competing *N*-arylation/vinylation and regioisomer formation are generally not problematic in these reactions.²⁵ As such, we examined the carboamination reaction of *N*-Boc protected substrates for the formation of piperidines.

Boc-protected amine substrate **II-33** was initially examined in the Pd-catalyzed carboamination reaction to afford piperidine **II-69**. We initially screened bidentate and monodentate ligands with 4-bromo-*t*-butylbenzene as the aryl halide, Pd(OAc)₂ as the precatalyst, and NaOtBu as the base. This initial optimization demonstrated the superior reactivity of P(2-fur)₃, while DPE-phos and dppe provided modest conversions to the piperidine. Heck side product **II-70** and trimer side product **II-71** as well as a mixture of unidentified side products were also observed.

Table 4. Carboamination of **II-33** with 4-Br-*t*Bu-benzene: Optimization of Reaction Conditions^a



Ar = *p*-*t*BuC₆H₄

LIGAND		NMR RATIOS			
% conversion	Piperidine (II-69)	Heck (II-70)	Trimer (II-71)	(unidentified) ^b	
DPE-phos	100	14	29	18	39
dppe	100	20	28	42	10
P(2-fur) ₃	100	65	35	0	0

^aConditions: 1.0 equiv amine, 1.2 equiv ArBr, 2.0 equiv NaOtBu, 6 mol % Pd₂(OAc), 8 mol % PPh₃, toluene (0.2–0.5M), 90 °C, 8–10 h; the reaction times have not been minimized. ^bAn unidentified mixture of products was observed by crude ¹H NMR and is represented by this number.

Various monodentate ligands were then screened for the related reaction of **II-33** with 2-bromonaphthalene and we found that PPh₃ was the optimal ligand in this coupling (Table 5). Amino olefin **II-33** was converted in moderate yield (63%) to piperidine **II-72** under these conditions. Minor amounts of the Heck product **II-73** and unidentified

products were also observed. Use of Pd(OAc)₂ as the precatalyst was superior to Pd₂(dba)₃ in the Boc-protected amine cyclizations for the synthesis of piperidines. Other reaction parameters, such as lowering the reaction temperature to 60 °C or 80 °C led to increased amounts of the Heck product **II-73** as well as trimer **II-71**. Increasing the amount of aryl halide (2.0 eq) did not lead to an improvement in the reaction conditions. Decreasing the amount of base led to increased Heck product. Therefore, the reaction conditions (1.0 equiv amine, 1.2 equiv ArBr, 2.0 equiv NaOtBu, toluene (0.2–0.5M), 90 °C) described in Table 5 were utilized in examining the scope of the reaction.

Table 5. Carboamination of **II-33** with 2-Br-Naphthalene: Optimization of Reaction Conditions^a

LIGAND	% conversion	Piperidine (II-72) ^b	Heck (II-73)	Trimer (II-71)	N-Arylation (II-74)	(unidentified) ^c
P(2-fur) ₃	100	49 (24)	42	9	0	0
PCy ₃	88	49	2	49	0	0
PMe ₃ ·HBF ₄	100	0	2	48	16	34
PPh ₃	100	79 (63)	6	0	0	15
P(<i>t</i> -Bu) ₂ Me	100	44	0	27	0	29
P[(<i>p</i> -OMe)C ₆ H ₄] ₃	100	59	0	0	26	15
PMePh ₂	100	21	0	68	11	0
Ph ₃ As	100	16	62	13	0	9

^aConditions: 1.0 equiv amine, 1.2 equiv ArBr, 2.0 equiv NaOtBu, 6 mol % Pd₂(OAc)₂, 8 mol % monodentate ligands, toluene (0.2–0.5M), 90 °C, 8–10 h; the reaction times have not been minimized.

^bThe yield in parentheses denotes the isolated yield. ^cAn unidentified mixture of products was observed by crude ¹H NMR and is represented by this number.

The catalyst loading and effect of varying the metal to phosphine ratio was also examined using the optimal conditions. Use of 6 mol % catalyst was necessary since use of less catalyst (2 mol %) with the same phosphine to metal ratio resulted in mainly trimer **II-71** formation (71%)²⁶ and minor amounts of the desired piperidines (29%). Increasing the concentration and reducing the catalyst to 3 mol % (4 mol % phosphine) led to greater amounts of the piperidine product, but still competing trimer formation (**II-71**) and Heck reaction (**II-73**) was problematic. Therefore, 6 mol% Pd(OAc)₂ catalyst

was necessary for the reaction to proceed optimally. The phosphine to metal ratio was also examined. The optimal phosphine to metal ratio was 1.3:1 as shown in Table 6. Use of more phosphine did not increase reaction efficiency, but use of less phosphine greatly inhibited the cyclization to **II-72**.

Table 6. Carboamination of **II-33** with 2-Br-Naphthalene: Optimization of Phosphine: Metal Ratio^a

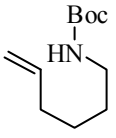
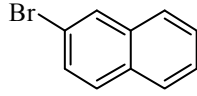
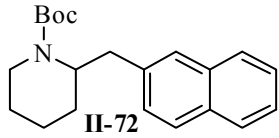
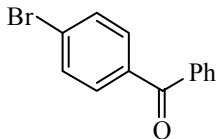
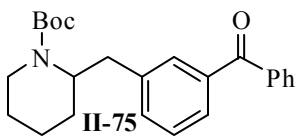
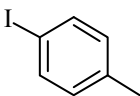
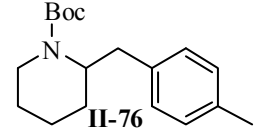
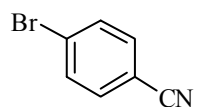
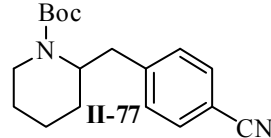
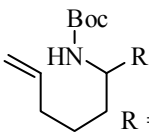
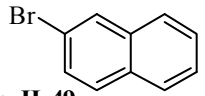
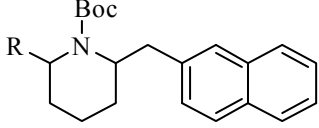
LIGAND	% conversion	Piperidine (II-72) ^b	Heck (II-73)	Trimer (II-71)	N-Arylation (II-74)	NMR RATIOS (unidentified) ^c
PPh ₃ (10 mol%)	100	74 (59)	9	0	0	17
PPh ₃ (8 mol%)	100	79 (63)	6	0	0	15
PPh ₃ (6 mol %)	100	66	17	5	0	12
PPh ₃ (4 mol %)	100	48	31	6	0	15
PPh ₃ (2 mol %)	100	23	40	7	0	30

^aConditions: 1.0 equiv amine, 1.2 equiv ArBr, 2.0 equiv NaOtBu, 6 mol % Pd₂(OAc), various mol % PPh₃, toluene (0.4 M), 90 °C, 8–10 h; the reaction times have not been minimized.

The scope of aryl bromides in the cyclization of **II-33** was briefly examined (Table 7). In most cases, the ¹H NMR spectrum of crude reaction mixtures was relatively clean, but the yields were moderate. This suggested that substrate **II-33** could be decomposing to volatile materials.²⁷ This methodology is currently limited to the synthesis of monosubstituted piperidines, as substituted substrates (Entry 5) did not

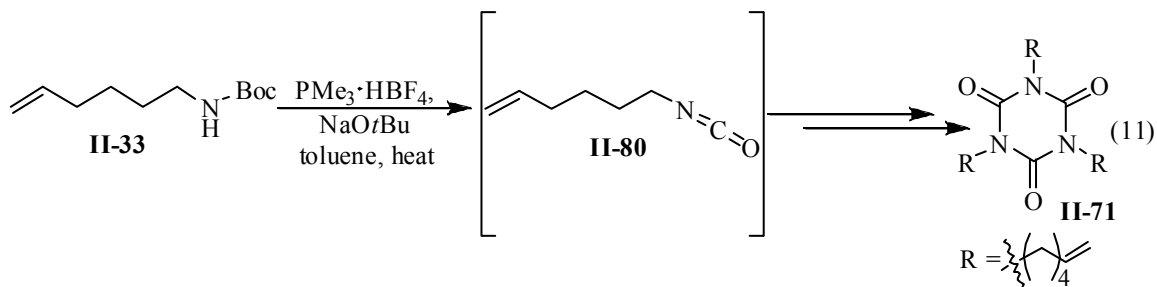
undergo cyclization under the optimized conditions and instead provided Heck byproducts.

Table 7. Carboamination of **II-33**, **II-49**, **II-54** with Aryl Halides^{a,f}

Entry	Substrate	Aryl-X	Product	Yield
1	 II-33		 II-72	64% ^b
2			 II-75	50%
3			 II-76	46% ^{c, d}
4			 II-77	50%
5	 R = Ph, II-49 R = Me, II-54		 R = Ph, II-78 R = Me, II-79	0% ^e

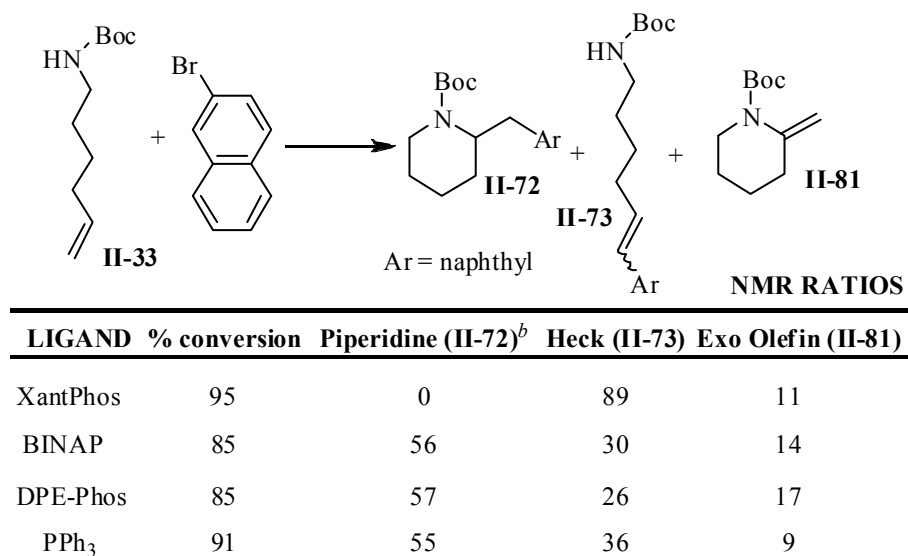
^aConditions: 1.0 equiv amine, 1.2 equiv ArBr, 2.0 equiv NaOtBu, 6 mol % Pd(OAc)₂, 8 mol % PPh₃ (entries 1, 2, 4) or P(2-furyl)₃ (entry 3), toluene (0.2–0.5M), 105 °C, 8–10 h. ^bA 10% unidentifiable material was inseparable from the pure product. ^c4-iodo-toluene used as aryl halide. ^d2.0 equiv ArBr, 2.0 equiv NaOtBu, 6 mol % Pd(OAc)₂, 8 mol % PPh₃. ^ePd₂(dba)₃ or Pd(OAc)₂, various ligands. ^fYields represent results of a single experiment.

The competing formation of **II-71** presumably arises from trimerization of isocyanate **II-80** (eq 11). Generation of isocyanates from decomposition of secondary carbamates under basic condition has been previously described.²⁸



A possible solution to Boc-decomposition would be to conduct these cyclizations with milder bases, and prior studies in our research group demonstrated that Cs_2CO_3 was effective in pyrrolidine-forming reactions.²⁴ Therefore, we turned our attention to screening the mild base Cs_2CO_3 in dioxane solvent with various ligands for the conversion of **II-33** to **II-72**. We found that while the product was generated under these conditions, continued screening and perhaps catalyst design would be necessary to fully optimize this reaction. We also observed Heck product **II-73** in this transformation as well as *N*-vinyl piperidine **II-81**. We also screened other solvents (in combination with various ligands) with the mild base conditions (Cs_2CO_3); however, THF, DMF, *t*BuOH, and DMA did not provide any of the desired piperidine **II-72** and Heck product **II-73** as well as starting material **II-33** were recovered from all these reactions.

Table 8. Optimization of Carboamination of **II-33** with 2-Br-Naphthalene using Cs₂CO₃ in Dioxane Solvent^a



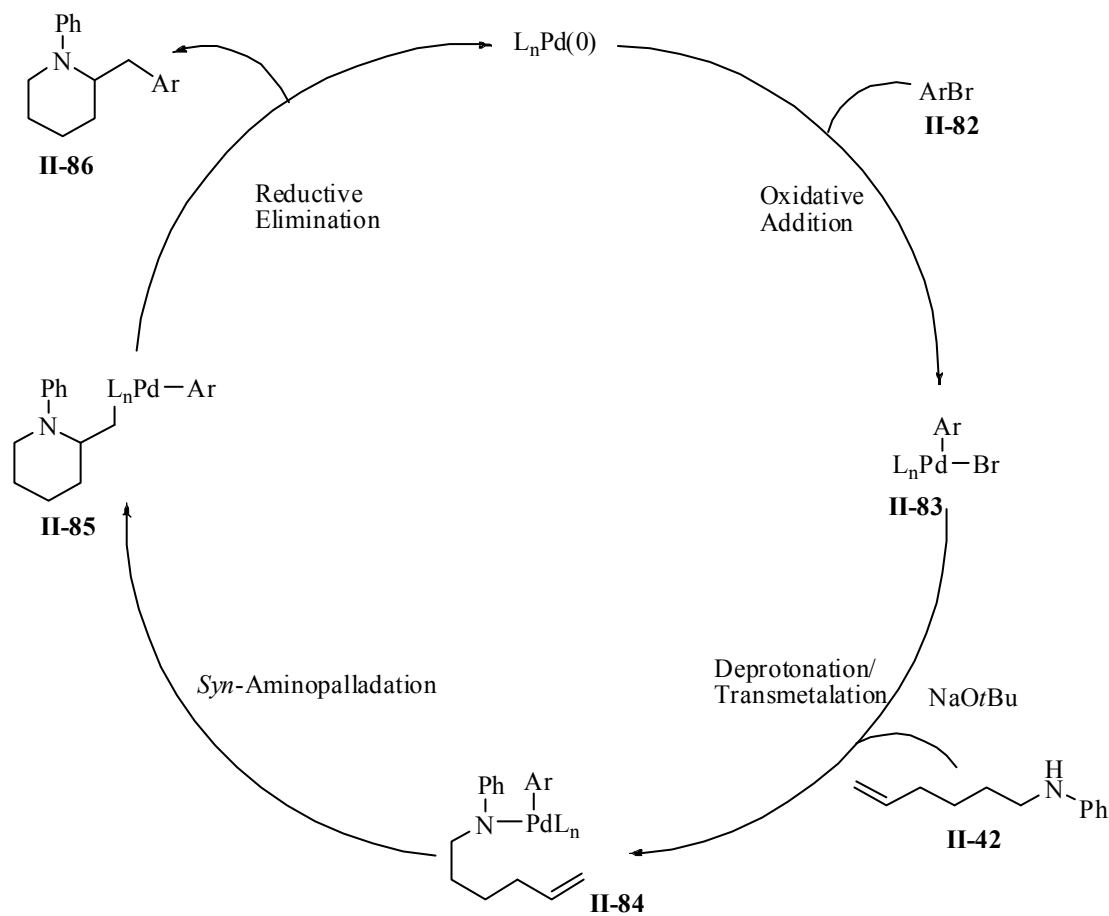
^aConditions: 1.0 equiv amine, 1.2 equiv ArBr, 2.3 equiv Cs₂CO₃, 6 mol % Pd₂(OAc)₂, 4 mol % monodentate ligand or 2 mol % bidentate ligand, dioxane (0.2 M), 100 °C, 8–10 h; the reaction times have not been minimized.

Preliminary experiments suggest that Boc decomposition was not a problem in these cases, but a general catalyst system for the formation of various Boc-protected analogs has not been identified with yields varying widely in these cases. Additionally, attempts to probe the stereoselectivity of these reactions by installing a substituent in the α position in the amine starting material proved futile and instead led to mixtures of Heck product as well as Boc-deprotection/*N*-arylation of the starting material. Use of Cs₂CO₃ provided trace amounts of the desired product in these substituted systems. Preliminary experiments utilizing mild base conditions (Pd(OAc)₂/DPE-Phos/Cs₂CO₃/dioxane/2-bromo-naphthalene) resulted in minor amounts of desired product **II-72**, Heck side products (*cis* and *trans*) **II-73**, and exo olefin side product **II-81** resulting from β -hydride elimination prior to reductive elimination.

Discussion

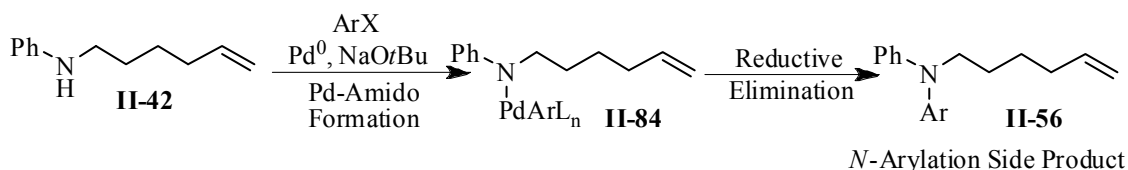
The mechanism for the piperidine-forming reactions is likely analogous to the pyrrolidine-forming reactions discussed in Chapter I. Oxidative addition of the aryl halide **II-82** to Pd(0) provides the electrophilic oxidative addition species **II-83**. Coordination of amine **II-42** followed by deprotonation affords Pd-amido complex **II-84**. Insertion of the olefin into the Pd–N bond, affords **II-85**, which undergoes reductive elimination to provide **II-86**.

Scheme 14. Proposed Catalytic Cycle for Piperidine Formation



Various side products are observed in the *N*-aryl and *N*-Boc piperidine-forming reactions. In the case of the *N*-aryl piperidine forming reactions, the *N*-arylation side product **II-56** is likely generated from the Pd-amido species (Scheme 15). Reductive elimination of the Pd-amido species **II-84** provides *N*-arylation side product **II-56**.

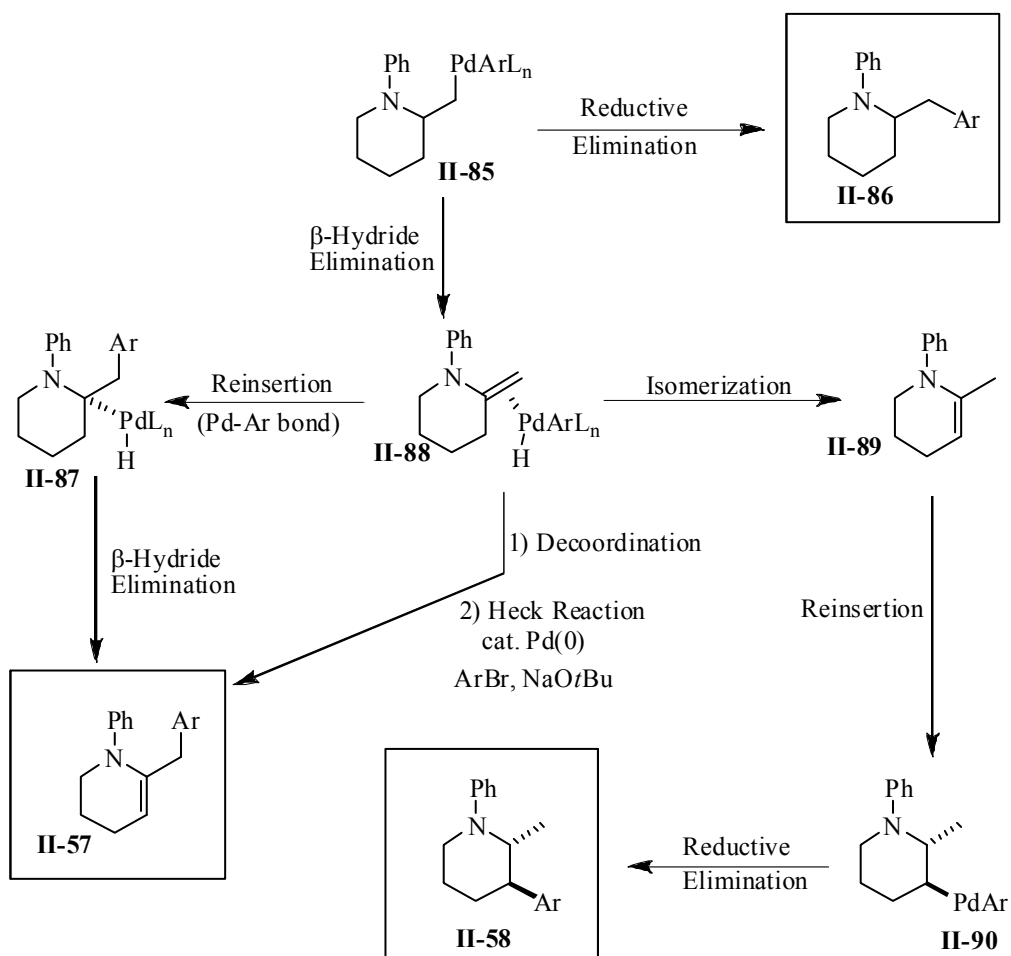
Scheme 15. Origin of *N*-Arylation Side Product (**II-56**)



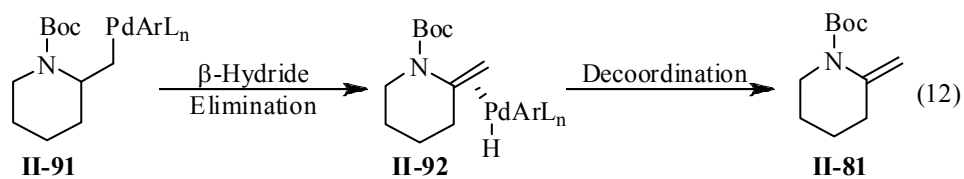
The structure of side product **II-57** has been tentatively assigned on the basis of ^1H NMR analysis of an isolated derivative (**II-57b**) which contained a 33% impurity. In addition, comparison to other similar side products studied in our group also led to the assignment (see Chapter III). Attempted isolation of side product **II-58** by column chromatography was not successful. The structure of side product **II-58** has therefore been tentatively assigned on the basis of ^1H NMR analysis of crude reaction mixtures and comparison to other reactions studied in our group. As shown in Scheme 16, these side products are likely generated from β -hydride elimination of intermediate **II-85** to provide exo-olefin piperidine **II-88**. A Heck reaction on intermediate **II-88** could provide side product **II-57**. Alternatively, side product **II-57** could arise from carbopalladation of exo-olefin **II-88**, to provide **II-87**, which could then undergo β -hydride elimination to provide side product **II-57**. This later pathway is less likely since insertion into Pd–H bonds is typically faster than insertion into Pd–C bonds.²⁹ Side product **II-58** is likely generated from isomerization of the Pd-aryl hydride species to intermediate **II-90**, which could then

undergo insertion with the opposite regiochemistry and β -hydride elimination to afford regioisomer **II-58**.

Scheme 16. Origin of Side Products **II-57** and **II-58**

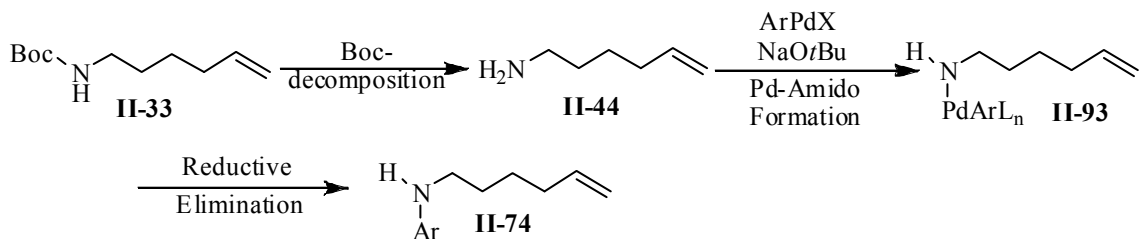


The common side products observed in the Boc-protected piperidine cyclizations presumably arise from the same type of intermediate as discussed above for the *N*-aryl piperidine series. Boc-piperidine intermediate **II-91** can undergo β -hydride elimination to provide exo-olefin side product **II-81** upon displacement of the metal from the double bond of **II-92**.



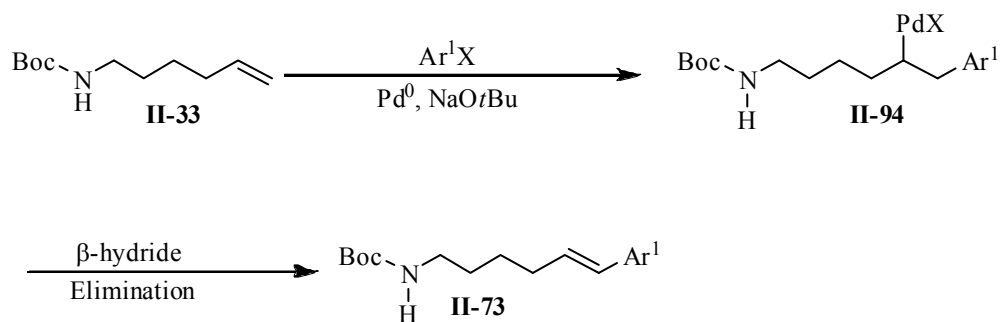
It is likely that the *N*-arylation side product **II-74** results from the primary amine **II-44** which is formed upon decomposition of the Boc-protecting group under the reaction conditions.²⁷ Pd-amido complex formation occurs to afford **II-93**, which upon reductive elimination provides the *N*-arylation side product **II-74**.

Scheme 17. Formation of *N*-Arylation Side Product **II-74** from Decomposition of **II-33**



Heck side product **II-73** is also observed in the cyclization of Boc-protected δ -amino olefins and likely forms from carbopalladation of **II-33** to provide **II-94**, followed by β -hydride elimination to product **II-73**.

Scheme 18. Formation of Heck Side Product **II-73** from **II-33**



The piperidine-forming carboamination reaction proceeds to provide the product in moderate yield. It is likely that these reactions are more difficult than the analogous five-membered ring formation to afford pyrrolidines because of the slower rate of cyclization. Formation of six-membered ring piperidines is more challenging than the five-membered ring pyrrolidines since the two ends of the γ -amino olefin are closer together than in a δ -amino olefin. Therefore, for entropic reasons the six-membered ring formation is less favorable and more likely to be outcompeted by other processes. Reactions of α -substituted *N*-aryl derivatives proceed to afford the desired product in low yield with modest levels of diastereoselectivity. The increase in side products in the reactions of substituted substrates is consistent with the hypothesis that the activation energy required to form the six-membered ring is higher than the analogous five-membered ring and anything done to slow the rate (i.e. placing substituents next a to nitrogen which slows Pd-amido formation) will likely thwart the reaction further.

The choice of $\text{P}(\text{2-fur})_3$ as the ligand in the majority of the *N*-aryl and PPh_3 as the ligand in the *N*-Boc piperidine-forming carboamination reactions discussed in this chapter is somewhat curious based on other carboaminations in our research lab, which

frequently utilize a bidentate chelating ligand. In addition to the monodentate nature of P(2-fur)₃, it is also a relatively small, electron poor ligand. It is possible that it may be easier to arrive at the key intermediates in a system that requires a greater degree of energy to cyclize if the ligand is small and can be easily displaced.

Conclusion

In conclusion, preliminary studies on the synthesis of piperidines via the Pd-catalyzed carboamination reaction were conducted. These transformations were more challenging than the analogous five-membered ring forming reactions that afford pyrrolidines. However, several monosubstituted 2-benzyl piperidines were generated in moderate yields. Further studies towards optimization of catalysts and conditions for these reactions will be necessary to broaden the scope of this important extension of our carboamination chemistry.

Experimental Section

General Considerations: All reactions were carried out under an argon or nitrogen atmosphere in oven- or flame-dried glassware. All catalysts, reagents, and aryl bromides were obtained from commercial sources and were used without further purification. *N*-(hex-5-enyl)aniline,²⁰ *tert*-butyl hex-5-enylcarbamate,²¹ *tert*-butyl hept-6-en-2-ylcarbamate²² were prepared according to published procedures or via minor modifications of literature procedures. Toluene, THF, ether, and dichloromethane were dried and purified using a GlassContour solvent purification system. Structural and stereochemical assignments were made on the basis of 2-D COSY, HSQC, and NOESY experiments. Ratios of diastereomers were determined by ¹H NMR and/or capillary GC analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ¹H NMR, GC, and/or combustion analysis, unless otherwise noted. The yields reported in the experimental and the tables describe the results of a single experiment, with the exception of Table 2, Entry 3, **II-66**, which is an average of two experiments. Thus, the yield in Table 2 (Entry 3) is different from the yield in the experimental for this example.

Synthesis of Substrates (Schemes 10–13)

General Procedure 1: Conversion of hex-5-en-1-amine (II-44) and 1-phenylhex-5-en-1-amine (II-48) to 4-(hex-5-enylamino)benzotrile (II-45) and 4-(1-phenylhex-5-enylamino)benzotrile (II-50). A flame dried Schlenk tube equipped with a magnetic stirbar was charged with Pd₂(dba)₃ (1 mol % complex, 2 mol % Pd), (±)-BINAP (2 mol

%), sodium *tert*-butoxide (1.2 equiv), the appropriate aryl bromide (1.0 equiv), and a 0.3–0.5 M solution of the primary amine (1.25–1.43 equiv) in toluene. The reaction mixture was heated to 60 °C or 80 °C with stirring until the starting material had been consumed as judged by NMR analysis (ca. 3.5 h–6 h). The mixture was cooled to rt and a solution of aqueous ammonium chloride was added (4 mL). The resulting mixture was extracted with ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

4-(Hex-5-enylamino)benzotrile (II-45). General procedure 1 was used for the *N*-arylation of hex-5-en-1-amine (**II-44**) (1.70 g, 17.14 mmol) with 4-bromobenzotrile (2.50 mg, 13.71 mmol) at 60 °C (3.5 h). This procedure afforded 2.74 g (80%) of the title compound as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.42 (d, *J* = 8.5 Hz, 2 H), 6.55 (d, *J* = 3.5 Hz, 2 H), 5.84–5.76 (m, 1 H), 5.04–4.97 (m, 2 H), 4.26 (s, 1 H), 3.15 (t, *J* = 7.0 Hz, 2 H), 2.13–2.08 (m, 2 H), 1.68–1.62 (m, 2 H), 1.53–1.47 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 151.6, 138.4, 133.9, 120.8, 115.2, 112.2, 98.5, 43.2, 33.5, 28.7, 26.4; IR (film) 3369, 2931, 2209, 1605 cm⁻¹. Anal. Calcd for C₁₃H₁₆N₂: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.93; H, 8.08; N, 13.74.

4-(1-Phenylhex-5-enylamino)benzotrile (II-50). General procedure 1 was used for the *N*-arylation of freshly distilled 1-phenylhex-5-en-1-amine (**II-48**) (3.14 g, 11.36 mmol) with 4-bromobenzotrile (1.45 g, 7.95 mmol) at 80 °C. This procedure afforded 2.00 g (91%) of the title compound as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.32

(m, 4 H), 7.29–7.24 (m, 3 H), 6.47 (d, $J = 8.4$ Hz, 2 H), 5.81–5.71 (m, 1 H), 5.02–4.96 (m, 2 H), 4.57 (m, 1 H), 4.36–4.31 (m, 1 H), 2.11–2.05 (m, 2 H), 1.88–1.76 (m, 2 H), 1.58–1.36 (m, 2 H). Anal. Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.56; H, 7.40; N, 9.98.

***tert*-Butyl 1-phenylhex-5-enylcarbamate (II-49).** A flask was charged with 1.17 g (6.67 mmol) of 1-phenylhex-5-en-1-amine (II-48),³⁰ diethyl ether (20 mL), and 1.29 g (5.94 mmol) of Boc-anhydride. The reaction was stirred for 12 h at room temperature. The crude material was diluted with ether (100 mL) and washed with 1 M NaOH, brine, and dried over Na_2SO_4 . The solvent was evaporated, and THF (100 mL) and 1 M NaOH (100 mL) were added and the mixture was stirred vigorously for 48 h. The compound was purified by flash chromatography to afford 1.14 g (70%) of the title compound. The compound was further recrystallized from 2.5% diethyl ether/hexanes to afford the pure product. 1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.30 (m, 3 H), 7.25–7.16 (m, 2 H), 5.82–5.68 (m, 1 H), 5.01–4.92 (m, 2 H), 4.79 (s, 1 H), 4.68–4.52 (m, 1 H), 2.09–2.02 (m, 2 H), 1.78–1.70 (m, 2 H), 1.43–1.28 (m, 11 H).

General Procedure for Pd-Catalyzed Synthesis of Aryl-Piperidines. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), $P(2\text{-furyl})_3$ (4 mol %), sodium *tert*-butoxide (2.0 equiv), and the aryl bromide (2.0 equiv). When dppe (2 mol %) was used as the ligand, $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), sodium *tert*-butoxide (2.0 equiv), and aryl bromide (2.0 equiv), were used. The Schlenk tube was purged with nitrogen and the amine was added as a solution in toluene (0.2–0.5 M substrate). The

Schlenk tube was then heated to 105 °C with stirring until the starting material had been consumed as judged by ¹H NMR analysis of an aliquot taken from the reaction mixture. The reaction mixture was then cooled to room temperature, saturated aqueous ammonium chloride (4 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

2-(4-Methylbenzyl)-1-phenylpiperidine (II-59). The reaction of 100 mg (0.57 mmol) of *N*-(hex-5-enyl)aniline (**II-42**) with 195 mg (140.3 μL, 1.14 mmol) of 4-bromotoluene was conducted for 12 h according to the general procedure. Upon purification, 103 mg (68%) of the title compound was obtained as a red solid, m.p. 50–55 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.38–7.33 (m, 2 H), 7.16–7.05 (m, 6 H), 6.89 (t, *J* = 7.5 Hz, 1 H), 4.09–4.04 (m, 1 H), 3.46–3.42 (m, 1 H), 3.10 (dt, *J* = 3.0, 11.4 Hz, 1 H), 2.88–2.80 (m, 1 H), 2.73–2.68 (m, 1 H), 2.38 (s, 3 H), 1.90–1.64 (m, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 151.2, 137.2, 135.5, 129.4, 129.24, 129.17, 118.9, 116.9, 58.4, 44.1, 32.7, 26.6, 25.9, 21.2, 19.2; IR (film) 2932, 1597 cm⁻¹. Anal. Calcd for C₁₉H₂₃N: C, 85.99; H, 8.74; N, 5.28. Found: C, 86.02; H, 8.69; N, 5.11.

2-(4-*tert*-Butylbenzyl)-1-phenylpiperidine (II-60). The reaction of 100 mg (0.57 mmol) of *N*-(hex-5-enyl)aniline (**II-42**) with 243 mg (199 μL, 1.14 mmol) of 4-bromo-*t*-butylbenzene was conducted for 12 h according to the general procedure. Upon purification, 140 mg (80%) of the title compound was obtained as an orange solid. This material was judged to be 90% pure and contained ca. 10% of side products **II-57b** and

II-58b, m.p. 37–42 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.33–7.29 (m, 4 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 7.01 (d, *J* = 8.0 Hz, 2 H), 6.84 (t, *J* = 7.2 Hz, 1 H), 4.07–4.04 (m, 1 H), 3.43–3.40 (m, 1 H), 3.07 (dt, *J* = 2.4, 11.2 Hz, 1 H), 2.85–2.79 (m, 1 H), 2.69–2.65 (m, 1 H), 1.86–1.72 (m, 2 H), 1.68–1.62 (m, 4 H) 1.33 (s, 9 H). ¹³C NMR (100 MHz, CDCl₃) δ 151.2, 148.9, 137.2, 129.4, 129.0, 125.4, 118.9, 116.8, 58.2, 44.0, 34.6, 32.7, 31.6, 26.7, 26.0, 19.2; IR (film) 2949, 1597 cm⁻¹. Anal. Calcd for C₂₂H₂₉N: C, 85.94; H, 9.51; N, 4.56. Found: C, 85.78; H, 9.56; N, 4.46.

6-(4-*tert*-Butylbenzyl)-1-phenyl-1,2,3,4-tetrahydropyridine (side product II-57b).

¹H NMR (400 MHz, CDCl₃) δ 7.25–7.18 (m, 6 H), 7.10 (t, *J* = 7.2 Hz, 1 H), 6.95 (d, *J* = 8 Hz, 2 H), 4.90 (t, *J* = 6.6 Hz, 1 H), 3.65–3.60 (m, 2 H), 3.23 (s, 2 H), 2.10–2.05 (m, 2 H), 1.70–1.55 (m, 2 H), 1.28 (s, 9H).

2-(Naphthalen-2-ylmethyl)-1-phenylpiperidine (II-55). The reaction of 90 mg (0.513 mmol) of *N*-(hex-5-enyl)aniline (**II-42**) with 213 mg (1.03 mmol) of 2-bromonaphthalene was conducted for 12 h according to the general procedure using 2 mol % dppe in place of P(2-furyl)₃. Upon purification, 111 mg (72%) of the title compound was obtained as a red solid. This material was judged to be 90% pure and contained ca. 10% of side products **II-57** and **II-58**, m.p. 80–89 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.82–7.76 (m, 3 H), 7.57 (s, 1 H), 7.49–7.41 (m, 2 H), 7.36–7.32 (m, 2 H), 7.29–7.26 (m, 1 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 6.87 (t, *J* = 7.2 Hz, 1 H), 4.17–4.13 (m, 1 H), 3.43–3.39 (m, 1 H), 3.12 (dt, *J* = 3.2, 11.6 Hz, 1 H), 3.03–2.97 (m, 1 H), 2.88–2.84 (m, 1 H), 1.88–1.77 (m, 2 H), 1.75–1.62 (m, 4 H); ¹³C NMR (100 MHz, CDCl₃) δ 151.2, 137.9, 133.8, 132.2,

129.4, 128.2, 127.9, 127.8, 127.6, 126.3, 126.1, 125.4, 119.2, 117.1, 58.4, 44.2, 33.4, 26.7, 26.0, 19.3; IR (film) 3054, 2930, 1597 cm^{-1} . MS (ESI) 302.1896 (302.1909 calcd for $\text{C}_{22}\text{H}_{23}\text{N}$, $\text{M} + \text{H}^+$).

2-(4-Methoxybenzyl)-1-phenylpiperidine (II-61). The reaction of 100 mg (0.57 mmol) of *N*-(hex-5-enyl)aniline (**II-42**) with 213 mg (143 μL , 1.14 mmol) of 4-bromoanisole was conducted for 12 h according to the general procedure. Upon purification, 101 mg (63%) of the title compound was obtained as a white solid, m.p. 60–62 $^{\circ}\text{C}$. ^1H NMR (300 MHz, CDCl_3) δ 7.32–7.26 (m, 2 H), 7.06–6.98 (m, 4 H), 6.86–6.81 (m, 3 H), 4.03–3.96 (m, 1 H), 3.79 (s, 3 H), 3.41–3.36 (m, 1 H), 3.10–3.01 (m, 1 H), 2.81–2.73 (m, 1 H), 2.66–2.61 (m, 1 H), 1.85–1.60 (m, 6 H); ^{13}C NMR (75 MHz, CDCl_3) δ 158.0, 151.2, 132.4, 130.2, 129.4, 118.9, 116.9, 114.0, 58.5, 55.4, 44.1, 32.3, 26.6, 25.9, 19.2; IR (film) 2933, 1597, cm^{-1} . MS (ESI) 282.1846 (282.1858 calcd for $\text{C}_{19}\text{H}_{23}\text{NO}$, $\text{M} + \text{H}^+$).

2-[(6-Methoxynaphthalen-2-yl)methyl]-1-phenylpiperidine (II-62). The reaction of 100 mg (0.57 mmol) of *N*-(hex-5-enyl)aniline (**II-42**) with 270 mg (1.14 mmol) of 2-bromo-6-methoxynaphthalene was conducted for 12 h according to the general procedure. Upon purification, 101 mg (54%) of the title compound was obtained as a red solid, m.p. 120–123 $^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 7.72–7.68 (m, 2 H), 7.52 (s, 1 H), 7.38–7.33 (m, 2 H), 7.27 (dd, $J = 1.6, 8.4$ Hz, 1 H), 7.19–7.14 (m, 2 H), 7.09–7.07 (m, 2 H), 6.89 (t, $J = 7.6$ Hz, 1 H), 4.17–4.13 (m, 1 H), 3.94 (s, 3 H), 3.43 (dd, $J = 4, 12$ Hz, 1 H), 3.12 (dt, $J = 3.2, 12$ Hz, 1 H), 3.01–2.95 (m, 1 H), 2.86–2.82 (m, 1 H), 1.90–1.78 (m, 2 H), 1.76–1.63 (m, 4 H). ^{13}C NMR (100 MHz, CDCl_3) δ 157.4, 151.2, 135.5, 133.2,

129.4, 129.3, 129.0, 128.4, 127.4, 127.0, 119.1, 118.9, 117.0, 105.8, 58.4, 55.4, 44.2, 33.2, 26.7, 26.0, 19.3; IR (film) 2935, 1597 cm^{-1} . MS (ES) 332.2010 (332.2014 calcd for $\text{C}_{23}\text{H}_{25}\text{NO}$, $\text{M} + \text{H}^+$).

Phenyl (4-[(1-phenylpiperidin-2-yl)methyl]phenyl) methanone (II-63). The reaction of 100 mg (0.57 mmol) of *N*-(hex-5-enyl)aniline (**II-42**) with 298 mg (1.14 mmol) of 4-bromobenzophenone was conducted for 12 h according to the general procedure. Upon purification, 114 mg (56%) of the title compound was obtained as a brown solid. The material was judged to be 95% pure, and contained ca. 5% of side product **II-56b**, m.p. 98–106 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.83–7.72 (m, 4 H), 7.61–7.56 (m, 1 H), 7.50–7.45 (m, 2 H), 7.32–7.21 (m, 4 H), 6.99 (d, $J = 9.0$ Hz, 2 H), 6.85 (t, $J = 7.5$ Hz, 1 H), 4.10–4.07 (m, 1 H), 3.41–3.37 (m, 1 H), 3.08 (t, $J = 10.8$ Hz, 1 H), 2.94–2.76 (m, 2 H), 1.85–1.64 (m, 5 H); ^{13}C NMR (75 MHz, CDCl_3) δ 196.5, 151.1, 145.7, 138.0, 135.5, 132.4, 130.5, 130.1, 129.4, 129.2, 128.4, 119.3, 117.1, 58.5, 44.2, 33.6, 27.0, 25.8, 19.2; IR (film) 2935, 1656, 1597 cm^{-1} . MS (ESI) 356.2014 (356.2014 calcd for $\text{C}_{25}\text{H}_{25}\text{NO}$, $\text{M} + \text{H}^+$).

4-(2-(Naphthalen-2-ylmethyl)piperidin-1-yl)benzotrile (II-64). The reaction of 100 mg (0.499 mmol) of 4-(hex-5-enylamino)benzotrile (**II-45**) with 207 mg (0.998 mmol) of 2-bromonaphthalene was conducted for 12 h according to the general procedure. Upon purification, 100 mg (61%) of the title compound was obtained as an orange solid, m.p. 145–153 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.82–7.77 (m, 3 H), 7.58 (s, 1 H), 7.49–7.43 (m, 4 H), 7.28 (d, $J = 8.0$ Hz, 1 H), 6.88 (d, $J = 8.0$ Hz, 2 H), 4.30 (s, 1 H), 3.66 (d, $J = 13.5$ Hz, 1 H), 3.17 (t, $J = 12.0$ Hz, 1 H), 3.10–3.03 (m, 1 H), 2.93–2.90 (m, 1 H), 1.88–

1.80 (m, 2 H), 1.70–1.61 (m, 4 H); ^{13}C NMR (125 MHz, CDCl_3) δ 153.2, 136.7, 134.5, 133.8, 133.7, 132.3, 128.5, 127.9, 127.7, 127.6, 126.4, 125.7, 120.6, 114.2, 98.9, 56.5, 42.3, 34.4, 26.4, 25.4, 18.7; IR (film) 2938, 2213, 1603 cm^{-1} . MS (ESI) 327.1873 (327.1861 calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2$, $\text{M} + \text{H}^+$).

4-[(2-(4-Methoxybenzyl)piperidin-1-yl]benzonitrile (II-65). The reaction of 94 mg (0.499 mmol) of 4-(hex-5-enylamino)benzonitrile (**II-45**) with 223 mg (125 μL , 0.998 mmol) of 4-bromoanisole was conducted for 12 h according to the general procedure. Upon purification, 98 mg (64%) of the title compound was obtained as a white solid, m.p. 96–101 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 7.45 (d, $J = 8.8$ Hz, 2 H), 7.06 (d, $J = 8.4$ Hz, 2 H), 6.84–6.80 (m, 4 H), 4.15–4.13 (m, 1 H), 3.78 (s, 3 H), 3.62 (d, $J = 11.6$ Hz, 1 H), 3.11 (dt, $J = 2.8, 12.4$ Hz, 1 H), 2.87–2.81 (m, 1 H), 2.72–2.68 (m, 1 H), 1.84–1.55 (m, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 158.3, 153.2, 133.7, 131.2, 130.2, 120.6, 114.2, 114.0, 98.6, 56.7, 55.4, 42.1, 33.3, 26.4, 25.4, 18.6; IR (film) 2935, 2213, 1603 cm^{-1} . MS (ES) 307.1803 (307.1810 calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}$, $\text{M} + \text{H}^+$).

4-[2-(4-*tert*-Butylbenzyl)piperidin-1-yl]benzonitrile (II-66). The reaction of 105 mg (0.524 mmol) of 4-(hex-5-enylamino)benzonitrile (**II-45**) with 223 mg (183 μL , 1.05 mmol) of 4-bromo-*t*-butylbenzene was conducted for 12 h according to the general procedure. Upon purification, 139 mg (80%) of the title compound was obtained as an orange solid, m.p. 95–98 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 7.45 (d, $J = 8.8$ Hz, 2 H), 7.31 (d, $J = 8.4$ Hz, 2 H), 7.10 (d, $J = 8.0$ Hz, 2 H), 6.82 (d, $J = 8.8$ Hz, 2 H), 4.22–4.20 (m, 1 H), 3.64 (d, $J = 12.4$ Hz, 1 H), 3.13 (dt, $J = 2, 12.4$ Hz, 1 H), 2.92–2.86 (m, 1 H),

2.77–2.72 (m, 1 H), 1.87–1.61 (m, 6 H), 1.34 (s, 9 H). ^{13}C NMR (100 MHz, CDCl_3) δ 153.2, 149.3, 136.0, 133.6, 128.9, 125.5, 120.5, 113.9, 98.4, 56.4, 42.0, 34.5, 33.7, 31.5, 26.5, 25.3, 18.5; IR (film) 2955, 2213, 1602 cm^{-1} . Anal. Calcd for $\text{C}_{23}\text{H}_{28}\text{N}_2$: C, 83.09; H, 8.49; N, 8.43. Found: C, 83.25; H, 8.72; N, 8.34.

(E)-4-(2-Cinnamylpiperidin-1-yl)benzotrile (II-67). The reaction of 50 mg (0.249 mmol) of 4-(hex-5-enylamino)benzotrile (**II-45**) with 91 mg (64 μL , 0.498 mmol) of β -bromo-styrene was conducted for 12 h according to the general procedure, 35 mg (49%) of the title compound was obtained as a yellow solid, m.p. 76–85 $^\circ\text{C}$. ^1H NMR (300 MHz, CDCl_3) δ 7.45 (d, $J = 9.3$ Hz, 2 H), 7.32–7.18 (m, 5 H), 6.83 (d, $J = 9.3$ Hz, 2 H), 6.42 (d, $J = 15.6$ Hz, 1 H), 6.12–6.02 (m, 1 H), 4.17–4.13 (m, 1 H), 3.64–3.59 (m, 1 H), 3.06 (dt, $J = 2.4, 12.6$ Hz, 1 H), 2.59–2.39 (m, 2 H), 1.86–1.74 (m, 2 H), 1.72–1.56 (m, 4 H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.3, 137.4, 133.7, 132.5, 128.7, 127.4, 127.1, 126.1, 120.6, 114.0, 98.5, 54.6, 42.0, 32.1, 27.4, 25.3, 18.6; IR (film) 2938, 2213, 1603 cm^{-1} . MS (ESI) 303.1838 (303.1861 calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2$, $\text{M} + \text{H}^+$).

(S, R)-4-[2-(4-tert-Butylbenzyl)-6-phenylpiperidin-1-yl]benzotrile (II-68). The reaction of 50 mg (0.181 mmol) of 4-(1-phenylhex-5-enylamino)benzotrile (**II-50**) with 4-bromo-*t*-butylbenzene 77.1 mg (63.2 μL , 1.14 mmol) was conducted for 12 h according to the general procedure. Upon purification, this procedure afforded 17 mg (24 %) of the title compound as a yellow oil. Crude ^1H NMR analysis of the reaction mixture indicated a 3:1 mixture of diastereomers (5.7:1 dr upon purification). Data are for the major isomer. ^1H NMR (400 MHz, CDCl_3) δ 7.44 (d, $J = 8.8$ Hz, 2 H), 7.34 (d, $J = 8.0$ Hz, 3 H), 7.27–7.25 (m, 3 H), 7.23–7.16 (m, 1 H), 7.10 (d, $J = 8.0$ Hz, 2 H), 6.93 (d, $J =$

8.8 Hz, 2 H), 4.73 (t, $J = 6.8$ Hz, 1H), 3.96–3.90 (m, 1 H), 2.94 (dd, $J = 3.2, 13.2$ Hz, 1 H), 2.59–2.53 (m, 1 H), 2.32–2.23 (m, 1 H), 2.08–2.00 (m, 1 H), 1.86–1.76 (m, 1 H), 1.72–1.67 (m, 2 H), 1.63–1.54 (m, 1 H), 1.32, (s, 9 H).

General Procedure for Pd-Catalyzed Synthesis of Boc-Piperidines. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with Pd(OAc)₂ (6 mol % complex, 6 mol % Pd), PPh₃ (8 mol %), sodium *tert*-butoxide (2.0 equiv), and the aryl bromide (1.2 equiv). The Schlenk tube was purged with nitrogen and the amine was added as a solution in toluene (0.2–0.5M). The Schlenk tube was then heated to 90 °C with stirring until the starting material has been consumed as judged by ¹H NMR analysis of an aliquot taken from the reaction mixture. The reaction mixture was then cooled to room temperature, saturated aqueous ammonium chloride (2–3 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

***tert*-Butyl 2-(naphthalen-2-ylmethyl)piperidine-1-carboxylate (II-72).** The reaction of 100 mg (0.502 mmol) of *tert*-butyl hex-5-enylcarbamate (II-33) with 125 mg (0.602 mmol) of 2-bromonaphthalene was conducted for 12 h according to the general procedure. Upon purification, 104 mg (64%) of the title compound was obtained as yellow solid, m.p. 84–89 °C. This material was obtained in ca. 90% purity. The identity of the impurity was not established. ¹H NMR (300 MHz, CDCl₃) δ 7.82–7.70 (m, 3 H), 7.62 (s, 1 H), 7.48–7.35 (m, 3 H), 4.46–4.60 (m, 1 H), 4.12–4.07 (m, 1 H), 3.09–2.92

(m, 3 H), 1.76–1.41 (m, 6 H), 1.31 (s, 9 H); ^{13}C NMR (75 MHz, CDCl_3) δ 155.1, 137.1, 133.8, 132.3, 128.1, 128.0, 127.75, 127.67, 127.6, 126.0, 125.4, 79.3, 52.5, 39.3, 36.4, 28.4, 27.2, 25.7, 19.2; IR (film) 2934, 1687 cm^{-1} . MS (ESI) 326.2121 (326.2120 calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_2$, $\text{M} + \text{H}^+$).

***tert*-Butyl 2-(4-benzoylbenzyl)piperidine-1-carboxylate (II-75)**. The reaction of 100 mg (0.502 mmol) of *tert*-butyl hex-5-enylcarbamate (**II-33**) with 162 mg (0.602 mmol) of 4-bromobenzophenone was conducted for 12 h according to the general procedure. Upon purification, 95 mg (50%) of the title compound was obtained as a viscous yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 7.77–7.72 (m, 4 H), 7.59–7.53 (m, 1 H), 7.47–7.42 (m, 2 H), 7.29 (d, $J = 8.4$ Hz, 2 H), 4.39–4.54 (m, 1 H), 4.06 (d, $J = 11.7$ Hz, 1 H), 3.03–2.78 (m, 3 H), 1.70–1.58 (m, 6 H), 1.33 (s, 9 H). ^{13}C NMR (75 MHz, CDCl_3) δ 196.3, 154.8, 144.6, 137.8, 135.5, 132.2, 130.3, 129.9, 129.2, 128.2, 79.2, 52.1, 39.0, 36.2, 28.3, 27.5, 25.5, 19.0; IR (film) 2934, 1687, 1659 cm^{-1} . MS (ESI) 402.2038 (402.2045 calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_3$, $\text{M} + \text{Na}^+$).

***tert*-Butyl 2-(4-methylbenzyl)piperidine-1-carboxylate (II-76)**. The reaction of 100 mg (0.502 mmol) of *tert*-butyl hex-5-enylcarbamate (**II-33**) with 218 mg (1.00 mmol) of 4-iodotoluene was conducted for 12 h according to the general procedure with the exception that 2.0 eq of 4-iodo toluene was used instead of 1.2 eq of the corresponding aryl bromide. Upon purification, 66 mg (46%) of the title compound was obtained as yellow solid, m.p. 33–35 $^\circ\text{C}$. ^1H NMR (300 MHz, CDCl_3) δ 7.13–7.00 (m, 4 H), 4.22–4.46 (m, 1 H), 4.03 (d, $J = 12.6$ Hz, 1 H), 2.95–2.69 (m, 3 H), 2.30 (s, 3 H), 1.68–1.39 (m, 6 H), 1.34 (s, 9 H). ^{13}C NMR (75 MHz, CDCl_3) δ 155.1, 136.4, 135.7, 129.3, 129.2,

79.2, 52.6, 39.2, 35.8, 28.5, 27.1, 25.8, 21.2, 19.1; IR (film) 2931, 1690 cm^{-1} . MS (ESI) 290.2112 (290.2120 calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_2$, $\text{M} + \text{H}^+$).

***tert*-Butyl 2-(4-cyanobenzyl)piperidine-1-carboxylate (II-77)**. The reaction of 100 mg (0.502 mmol) of *tert*-butyl hex-5-enylcarbamate (**II-33**) with 110 mg (0.602 mmol) of 4-bromobenzonitrile was conducted for 12 h according to the general procedure. Upon purification, 75 mg (50%) of the title compound was obtained as a yellow solid, m.p. 67–73 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.54 (d, $J = 8.4$ Hz, 2 H), 7.27 (d, $J = 7.8$ Hz, 2 H), 4.30–4.50 (m, 1 H), 4.02 (d, $J = 10.8$ Hz, 1 H), 3.01–2.72 (m, 3 H), 1.67–1.34 (m, 6 H), 1.28 (s, 9 H); ^{13}C NMR (75 MHz, CDCl_3) δ 154.8, 144.3, 132.2, 130.2, 119.1, 110.2, 79.5, 52.1, 39.2, 36.5, 28.4, 27.9, 25.6, 19.1; IR (film) 2935, 2227, 1686 cm^{-1} . MS (ESI) 355.1995 (355.1998 calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_2$, $\text{M} + \text{Na} + \text{MeOH}$).

References

- ¹ Nakhla, J. S.; Wolfe, J. P. *Unpublished Results*.
- ² (a) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcharding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989. (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729. (c) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813. (d) Davies, H. M. L.; Hansen, T.; Hopper, D. W.; Panaro, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 6509–6510. (e) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693–3712.
- ³ For isolation, see: (a) R. J. Highet. *J. Org. Chem.* **1964**, *29*, 471–474. For structure and configuration, see: (b) Rice, W. Y.; Coke, J. L. *J. Org. Chem.* **1966**, *31*, 1010–1012.
- ⁴ Ma, D.; Ma, N. *Tetrahedron Lett.* **2003**, *44*, 3963–3965.
- ⁵ Kim, G.; Kim, N. *Tetrahedron Lett.* **2007**, *48*, 4481–4483.
- ⁶ For isolation, see: Ladenburg, A.; Adam, G. *Chem. Ber.* **1891**, *24*, 1671–1676.
- ⁷ (a) Hedley, S. J.; Moran, W. J.; Prenzel, A. H. G. P.; Price, D. A.; Harrity, J. P. A. *Synlett* **2001**, 1596–1598. (b) Löfstedt, J.; Pettersson-Fasth, H.; Bäckvall, J. E. *Tetrahedron* **2000**, *56*, 2225–2230.
- ⁸ Cossy, J.; Willis, C.; Bellosta, V.; Bouzbouz, S. *Synlett* **2000**, 1461–1463.
- ⁹ Matsumura, Y.; Kanda, Y.; Shirai, K.; Onomura, O.; Maki, T. *Org. Lett.* **1999**, *1*, 175–178.
- ¹⁰ Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913–2916.
- ¹¹ Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzenberger, S. M.; Varga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682–6685.
- ¹² Sabat, M.; Johnson, C. R. *Tetrahedron Lett.* **2001**, *42*, 1209–1212.
- ¹³ Grandel, R.; Kazmaier, U.; Rominger, F. *J. Org. Chem.* **1998**, *63*, 4524–4528.
- ¹⁴ Fornicola, R. S.; Subburaj, K.; Montgomery, J. *Org. Lett.* **2002**, *4*, 615–617.
- ¹⁵ MacAlpine, I. J.; Armstrong, R. W. *Tetrahedron Lett.* **2000**, *41*, 1849–1853.
- ¹⁶ Zhang, X.; Jung, X. S.; Marino, P. S.; Fox, M. A.; Martin, P. S.; Merkert, J. *Tetrahedron Lett.* **1993**, *34*, 5239–5242.
- ¹⁷ Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Seiji, Y. *J. Org. Chem.* **1997**, *62*, 776–777.

- ¹⁸ Larock, R. C.; Yang, H.; Weinreb, S. M.; Herr, R. J. *J. Org. Chem.* **1994**, *59*, 4172–4178.
- ¹⁹ Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246–4247.
- ²⁰ Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1, 1377–1393.
- ²¹ Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246–4247.
- ²² Paek, S.-M.; Seo, S.-Y.; Min, K.-H.; Shin, D. M.; Chung, Y. K.; Suh, Y.-G. *Heterocycles* **2007**, *71*, 1059–1066.
- ²³ Some of the catalyst optimization, including the screening of other ligands was performed by another student and therefore is not included in this discussion.
- ²⁴ Bertrand, M. B.; Leathen, M. L.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 457–460.
- ²⁵ Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447–6459.
- ²⁶ This was established by ¹H NMR ratios.
- ²⁷ Tom, N. J.; Simon, W. M.; Frost, H. N. Ewing, M. *Tetrahedron Lett.* **2004**, *45*, 905–906.
- ²⁸ The cyclotrimerization of isocyanates has been previously reported, see: (a) Duong, H. A.; Cross, M. J.; Louie, J. *Org. Lett.* **2004**, *6*, 4679–4681. (b) Tang, J.; Mohan, T.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 4931–4938. (c) Laas, H.-J.; Halpaap, R.; Pedain, J.; Konig, K. U.S. 5,750,629, 1998.
- ²⁹ Alkene insertion into late M–H bonds is usually much faster than alkene insertion into late M–C bonds. See: (a) Brookhart, M.; Hauptman, E.; Lincoln, D. M. *J. Am. Chem. Soc.* **1992**, *114*, 10394–10401. (b) Siegbahn, P. E. M.; Stromberg, S.; Zetterberg, K. *Organometallics* **1996**, *15*, 5542–5550.
- ³⁰ Eddaif, A.; Laurent, A.; Mison, P.; Pellissier, N.; Carrupt, P. A.; Vogel, P. *J. Org. Chem.* **1987**, *52*, 5548–5560.

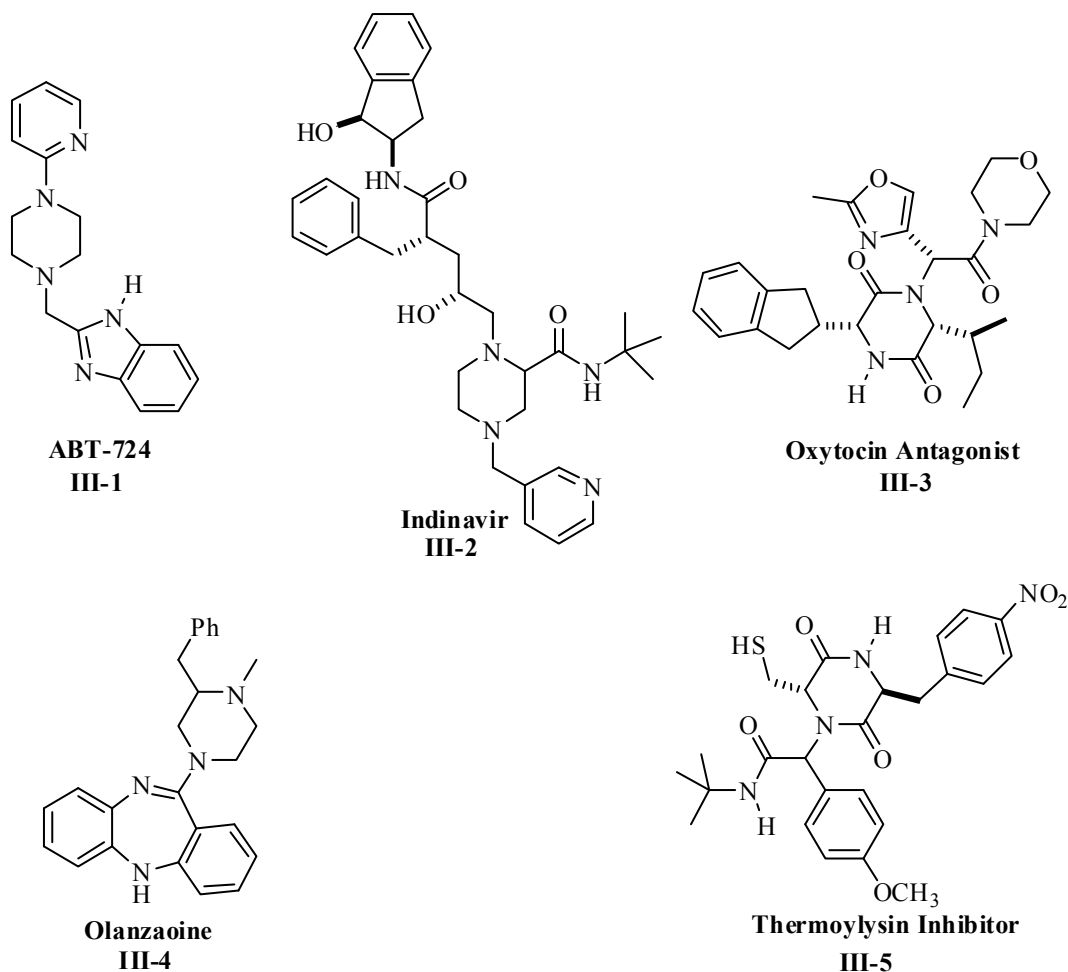
Chapter III

Carboamination Reactions for the Asymmetric Synthesis of Piperazines¹

Introduction: Biologically Active Piperazine Pharmaceuticals

Piperazines² are of profound importance in medicinal chemistry and drug development. A 2001 survey of biologically relevant templates in the MDDR revealed 2271 biologically active molecules that contained substituted *N*-aryl piperazines; 16 of these compounds were drugs on the market and an additional 23 were in phase II or III clinical trials.³ For example, ABT-724 (**III-1**) is a selective dopamine D4 receptor agonist that was developed by Abbott for treatment of erectile dysfunction.⁴ Indinavir (trade name Crixivan, (**III-2**)), is a popular HIV protease inhibitor developed by Merck and is very effective in preventing virus replication and minimizing HIV-related infections.⁵ Compound **III-3** is an oxytocin antagonist discovered by Glaxo-Smith-Kline.⁶ Olanzaoine⁷ (**III-4**) is among the several in the same class as the drug Olanzapine (trade name Zyprexa) which is an antipsychotic developed by Eli Lilly. Compound **III-5** is a thermolysin inhibitor developed by Affymetrix.

Figure 2. Piperazine Pharmaceuticals

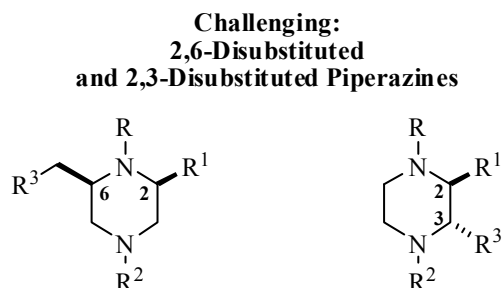


Methods for the Synthesis of 2,6-Disubstituted Piperazines

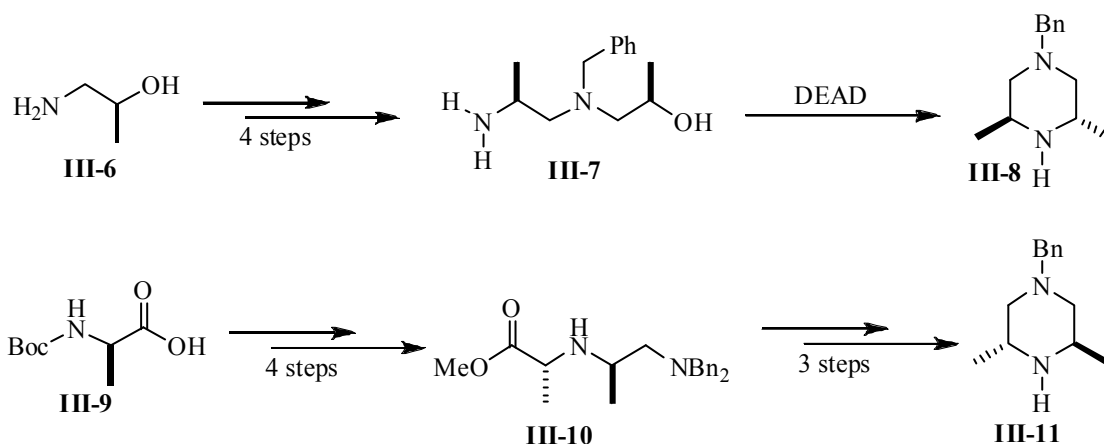
The presence of substituents on C2, C3, C5, and C6 (Figure 3) of the piperazine ring is known to have a significant influence on the biological activity of these molecules, and the ability to prepare substituted piperazines is of value for the optimization of biological properties.⁸ The asymmetric synthesis of monosubstituted or 2,5-disubstituted piperazines can be accomplished in a straightforward manner through coupling of readily available amino acids to provide diketopiperazines, which can then be reduced to piperazines.⁹ However, the stereoselective preparation of enantiomerically enriched 2,6-

disubstituted piperazines remains challenging, particularly when one of the substituents is not a carboxylic acid or ester. There are few asymmetric routes to *N,N*-disubstituted-2,6-dialkylpiperazines, and the existing syntheses of these molecules typically require ≥ 6 steps.^{10,11,12} For example, amino alcohol **III-6** was homologated in four steps to diamine **III-7** which was then treated with diethyl azodicarboxylate to afford disubstituted piperazine **III-8** (total 5 steps).^{10b,c} Similarly, Boc-alanine (**III-9**) could also be homologated to diamino ester **III-10** which in another three steps was converted to piperazine **III-11** (7 steps total).^{10b,c} This chemistry has only been used for the preparation of the dimethyl substituted piperazines shown below (Scheme 19).

Figure 3. Synthetically Challenging Substituted Piperazines

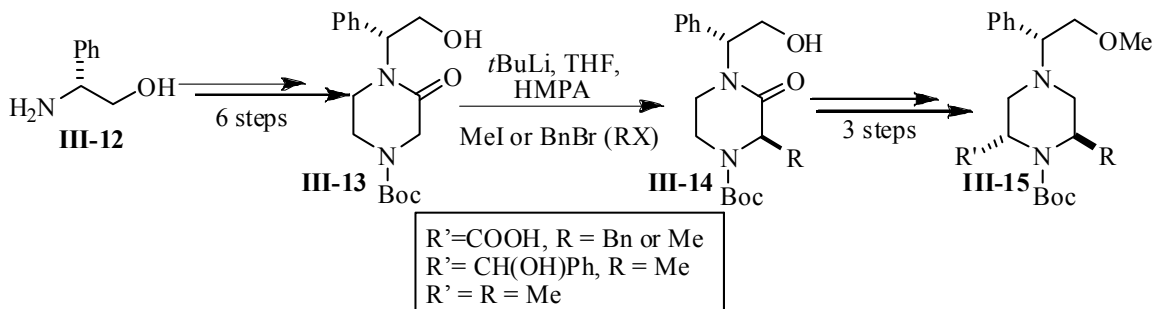


Scheme 19. Synthesis of 2,6-Dimethyl Piperazines



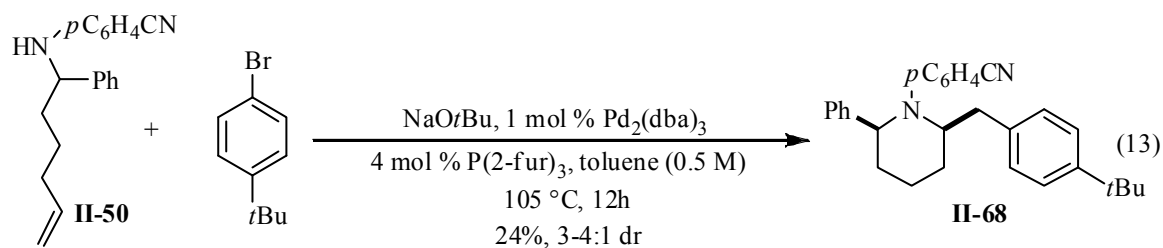
Another strategy that has been used to prepare 2,6-disubstituted piperazines involves construction of the core ring followed by alkylation.^{11a} For example, amino alcohol **III-12** was converted in six steps to piperazine-2-one **III-13**. This intermediate was then deprotonated with *t*-BuLi and then alkylated with reactive electrophiles to generate **III-14**. Protection of the hydroxyl group followed by a second metalation/alkylation sequence, and reduction of the carbonyl provided **III-15**. This sequence requires ten linear steps, and is limited in the types of substituents that can be placed in the 2 and 6 positions.

Scheme 20. Synthesis of 2,6-Disubstituted Piperazines

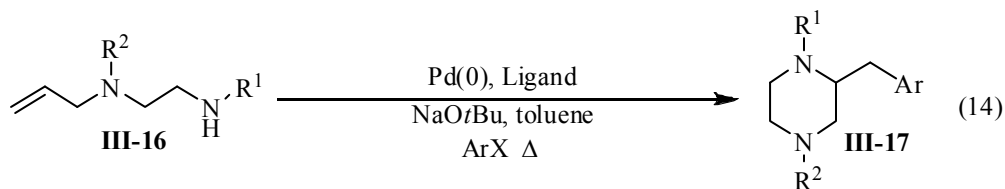


Introduction to Pd-Catalyzed Carboamination Reaction for the Synthesis of Piperazines

As described in Chapter II, our efforts to synthesize piperidines via Pd-catalyzed carboamination reactions demonstrated the feasibility of preparing six-membered rings with this method. However, in most cases, modest yields were obtained due to competing side reactions, and formation of 2,6-disubstituted products was very difficult (eq 13).



We reasoned that the intramolecular syn-aminopalladation step in the catalytic cycle might be slow relative to the analogous five-membered ring process due to entropy. We hypothesized that we could potentially circumvent the difficulties associated with an entropically slower transformation by installing an amine in the tether, which would assist in bringing the two ends of the molecule together, therefore facilitating the more challenging cyclization (eq 14).



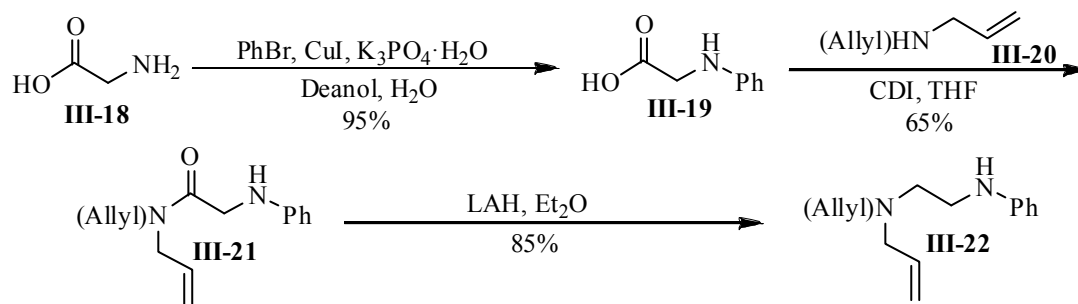
In addition to the potential synthetic utility of the above strategy, the key cyclization reaction is fundamentally interesting. The construction of heterocyclic rings bearing more than one nitrogen atom has not been achieved in Pd-catalyzed carboamination or carboetherification reactions between heteroatom-tethered olefins and aryl/alkenyl halides.

Preliminary Studies

In order to examine the feasibility of preparing substituted piperazines via Pd-catalyzed carboamination reactions, we synthesized ethylene diamine derivative **III-22** as shown in Scheme 21. Glycine was *N*-arylated with bromobenzene in the presence of CuI

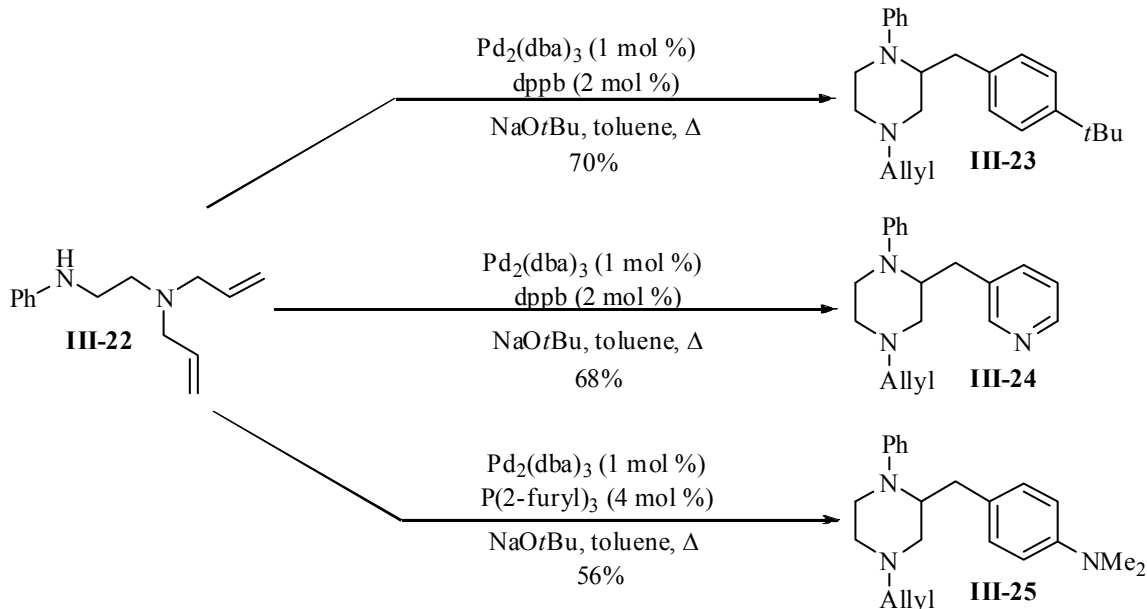
(to give **III-19**), followed by *N*-allyl amide formation and reduction to provide ethylene diamine **III-22**.

Scheme 21. Synthesis of *N*¹,*N*¹-Diallyl-*N*²-Phenylethane-1,2-Diamine



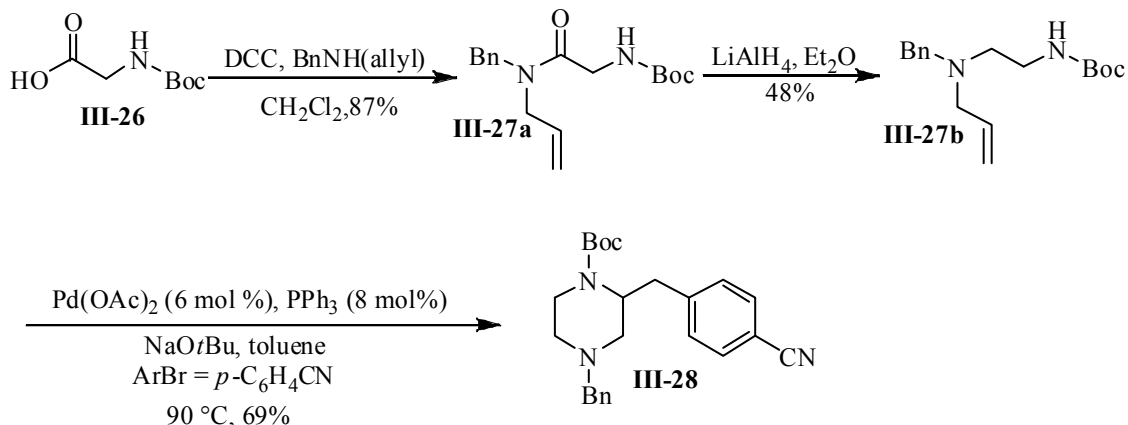
With **III-22** in hand, we surveyed reaction conditions that had been effective in related pyrrolidine and piperidine-forming reactions. We were gratified to find that use of a catalyst composed of $\text{Pd}_2(\text{dba})_3$ and dppb or $\text{P}(2\text{-fur})_3$ provided satisfactory results with several aryl bromide coupling partners (Scheme 22).

Scheme 22. Synthesis of Monosubstituted Piperazines



To determine whether other protecting groups on N1 would undergo the carboamination reaction, Boc-protected substrate **III-27** was prepared from Boc-glycine in two steps. This substrate underwent the carboamination reaction to provide piperazine **III-28** in good yield, further demonstrating the greater ease of cyclization of the 1,2-diamino olefins relative to the carbon analog. These results demonstrated the viability of this strategy for piperazine synthesis, and we set out to prepare more highly substituted derivatives.

Scheme 23. Synthesis of Monosubstituted Boc-Piperazines

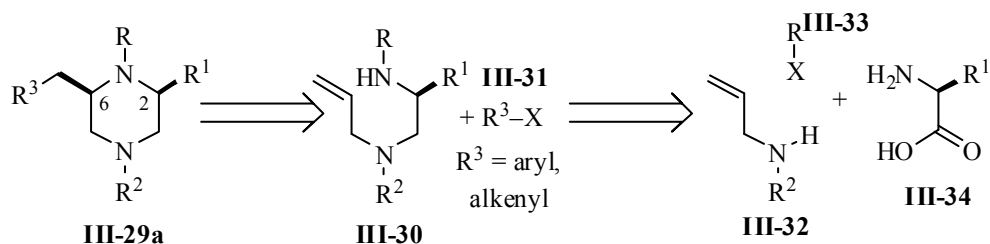


Potential Advantages and Challenges to Use of Carboamination Reactions for the Synthesis of 2,6-Disubstituted Piperazines

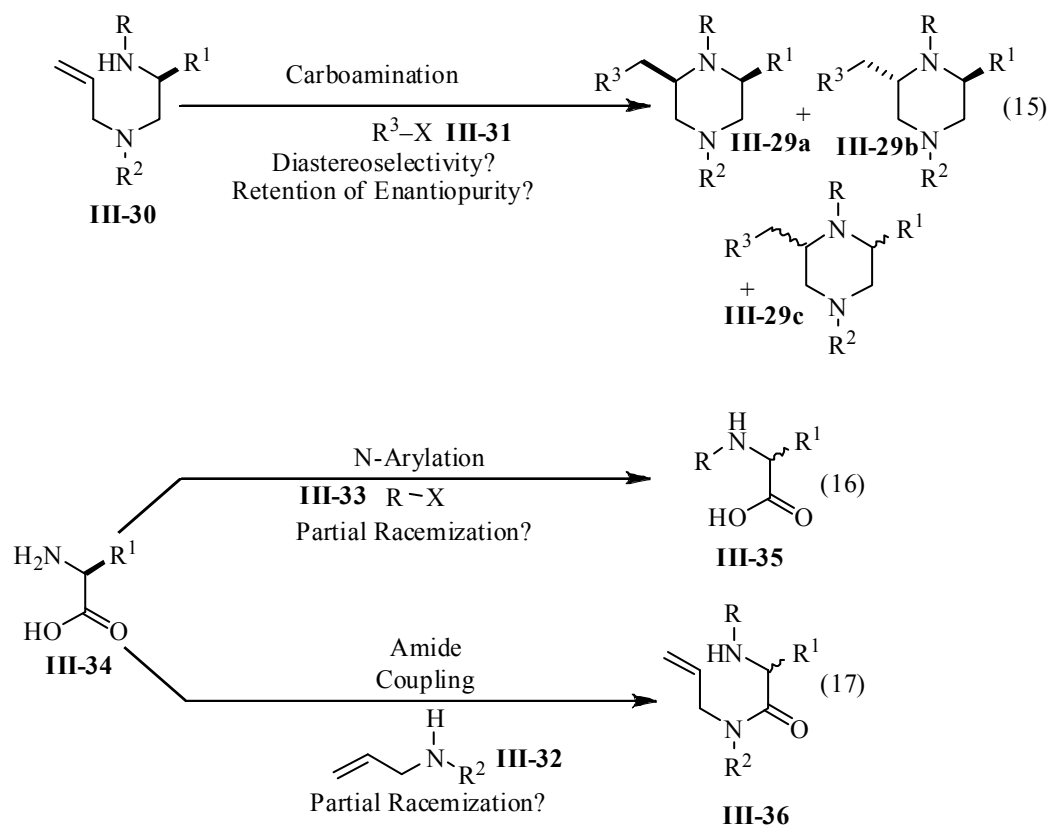
Due to the limitations associated with the stereoselective synthesis of 2,6-disubstituted piperidines (eq 13), we chose to examine the synthesis of these molecules using our Pd-catalyzed carboamination reaction. Our approach to the construction of 2,6-disubstituted piperazines **III-29a** is shown below (Scheme 24). The key Pd-catalyzed carboamination reaction is employed to generate the heterocyclic ring and form two bonds simultaneously.^{13,14} Retrosynthetic analysis of the requisite substrates (**III-30**) suggested these compounds could be prepared in a straightforward and modular fashion from simple precursors: amino acids, allylic amines, and aryl halides. Moreover, various aryl or vinyl halides ($\text{R}^3\text{-X}$) could be used in the key Pd catalyzed coupling reaction. All of these starting materials (**III-32**, **III-33**, and **III-34**) are readily available, and amino acids offer access to a cheap, extensive pool of chirality. This strategy allows for installation of many different groups in the 2- and 6- positions by simple modification of the amino acid precursor **III-34** and the aryl/alkenyl halide coupling partner (R^1 and R^3 of

III-34 and **III-31**, respectively). Additionally, the protecting groups on the amines could also be readily varied (R and R^2 of **III-33** and **III-32**, respectively), making the route both flexible and amenable to analog synthesis. Finally, the synthesis of **III-29a** would generate enantiopure products, provided the stereochemical integrity of the α -stereocenter is maintained throughout the course of the synthesis.

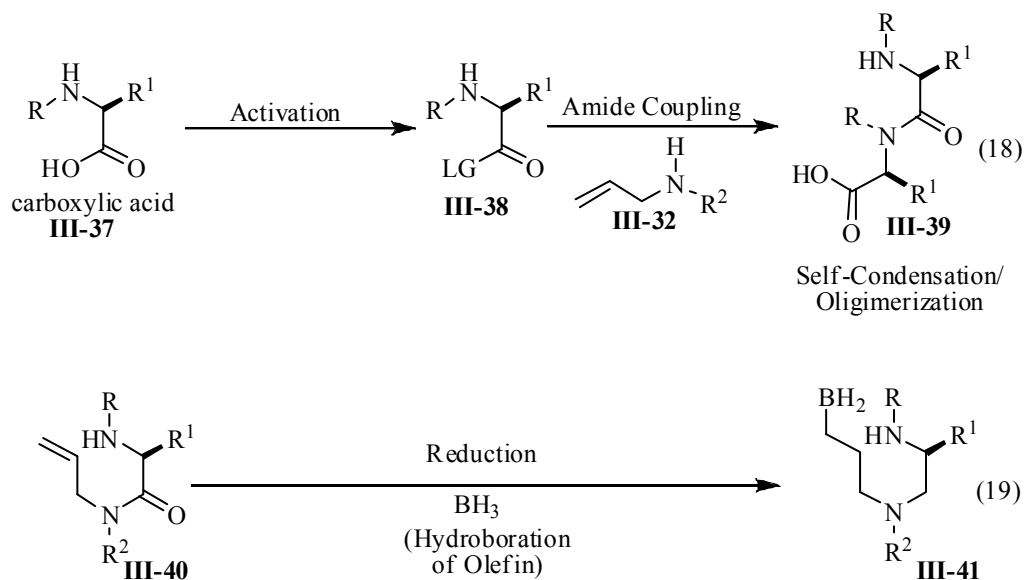
Scheme 24. Retrosynthetic Analysis for 2,6-Disubstituted Piperazines



While we believed this strategy could be very useful, we also felt there would be some challenges associated with the development of the chemistry. First and foremost, it was not clear whether the key reaction would be feasible since cyclization of the analogous α -substituted piperidine precursors (Chapter II) was difficult. Additionally, if in fact the reaction was successful, it was not clear whether the diastereoselectivity of the transformations would be high (eq 15). Additionally, it would be critical to employ tactics that would maintain the stereochemical integrity of the amino-acid derived structure (eq 15).¹⁵ It is well known that amino acids can be prone to partial racemization in *N*-arylation (eq 16) and amide-forming reactions (eq 17) under strongly basic and or high temperature conditions.¹⁵



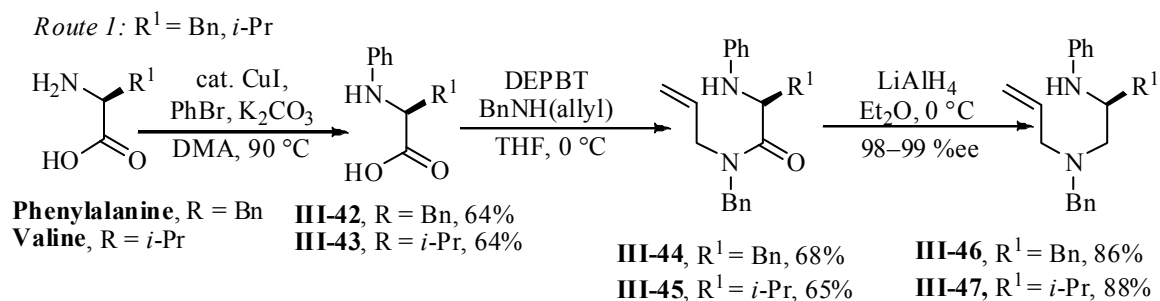
We were also concerned about difficulties that may arise during coupling of amines with *N*-aryl amino acids since the nucleophilic *N*-aryl amine moiety could undergo intermolecular addition to the activated intermediate to provide oligomers (eq 18). Finally, reductions of amides such as **III-40** are usually effected using BH_3 as the reducing agent,^{10b} and since the substrates for the carboamination reactions contain an olefin that would likely undergo hydroboration under these reaction conditions, it was necessary to find an appropriate reducing agent (eq 19).



Substrate Synthesis

The substrates for the carboamination reactions were prepared from commercially available amino acids by using one of two 3–4-step sequences. As shown in Scheme 25, the first route employs unprotected amino acid starting materials, which were subjected to Cu-catalyzed *N*-phenylation using the anhydrous conditions developed by Ma, to generate **III-42** and **III-43** without significant degradation of enantiomeric purity.¹⁶ However, attempts to use biphasic conditions¹⁷ for the *N*-arylation of unhindered amino acids such as alanine or phenylalanine provided products with low enantiomeric purity (ca. 14–50% ee). Amide bond formation was achieved via coupling of **III-42** and **III-43** with *N*-(benzyl)allylamine using Goodman's DEPBT reagent.¹⁸ Use of other peptide coupling reagents such as CDI or DCC/HOBT led to erosion of enantiomeric purity to afford products with 85–90% ee. Reduction of amides **III-44** and **III-45** with lithium aluminum hydride at 0 °C afforded **III-46** and **III-47** ($\text{R}^1 = \text{Bn}$ and $\text{R}^1 = i\text{-Pr}$), with 98%–99% ee.

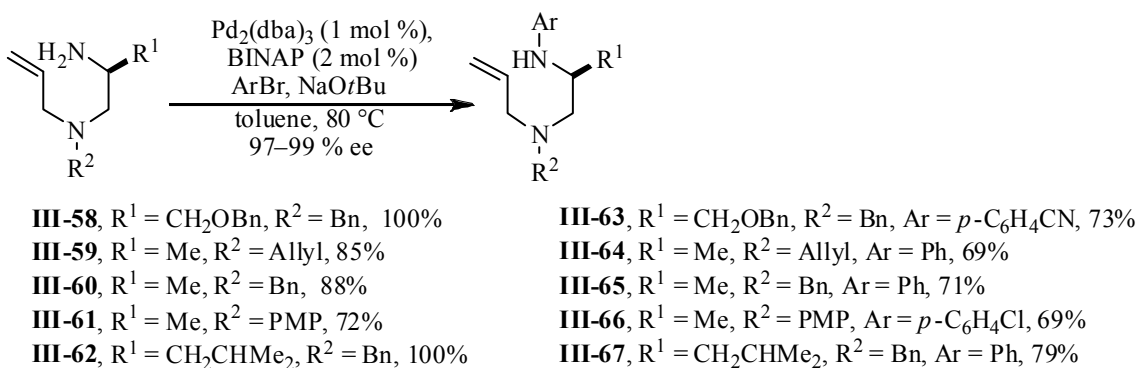
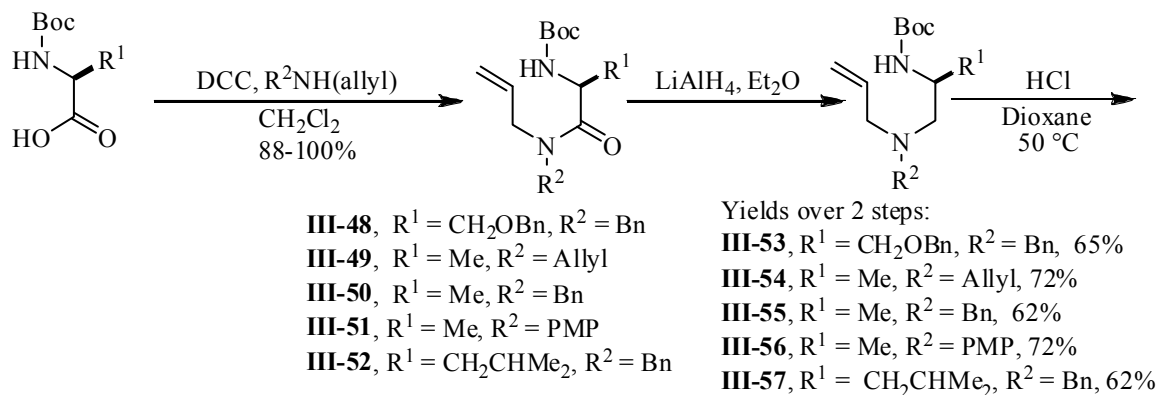
Scheme 25. Synthesis of Substrates for 2,6-Disubstituted Piperazine Synthesis I



Alternatively, in some instances it was advantageous to employ *N*-Boc-protected amino acids as starting materials due to their commercial availability, or due to partial loss of enantiomeric purity during the Cu-catalyzed *N*-arylation reaction.¹⁹ These starting materials were converted in two steps via DCC-mediated coupling with an allylic amine followed by reduction with LiAlH₄ at 0 °C (Scheme 26) to provide Boc-protected diamines **III-53-III-57**, which could be used as substrates for the carboamination reaction. If instead an *N*-arylated precursor was desired, cleavage of the Boc group was accomplished by treatment of intermediates **III-53-III-57** with HCl/dioxane, and subsequent Pd-catalyzed *N*-arylation²⁰ afforded the requisite substrates (**III-63-III-67**) in high enantiomeric purity. These two methods for the synthesis of the key precursors achieved and addressed the goals and challenges discussed above.

Scheme 26. Synthesis of Substrates for 2,6-Disubstituted Piperazine Synthesis II

Route 2: R¹ = Me, CH₂OBn



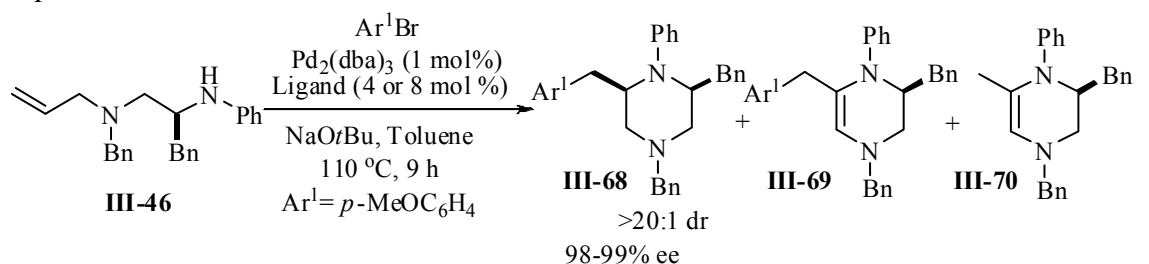
Catalyst Optimization

With suitable precursors in hand, we examined Pd-catalyzed reactions of phenylalanine-derived substrate **III-46** with 4-bromoanisole using a number of different phosphine ligands (Table 9). These reactions provided a mixture of three products: **III-68**, **III-69**, and **III-70**. In all cases, the desired product **III-68** was formed with >20:1 dr and retention of enantiomeric purity.

In contrast to the analogous 2,5-disubstituted pyrrolidine-forming cyclizations, which were effectively catalyzed by mixtures of Pd₂(dba)₃ and dppe or dppb,²¹ reaction of substituted diamines such as **III-46** were not efficient with these catalysts. Bidentate

ligands that are also effective in other carboamination reactions^{13a,c,d,f,g,22} such as Dpe-Phos and Xant-Phos were superior to dppe. However, use of catalysts supported by P(2-furyl)₃ provided the best results in the piperazine-forming reactions. Use of a 4:1 ratio of phosphine to palladium led to complete consumption of the diamine starting material, whereas reactions that employed a 2:1 L:Pd ratio frequently halted at ca. 85–90% conversion.²³ The reason behind the need for excess phosphine to provide consumption of starting material is not entirely clear, but this may help to stabilize the catalyst and increase turnover number.^{24,25}

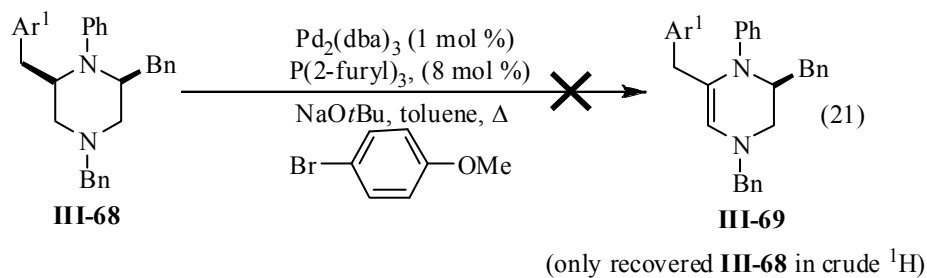
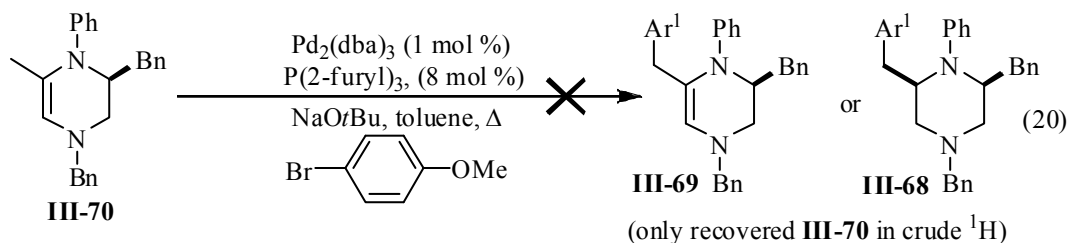
Table 9. Optimization of Carboamination Reaction for Synthesis of 2,6-Disubstituted Piperazines



LIGAND	% conversion	NMR RATIOS		
		Piperazine (III-68)	Side Product (III-69)	Side Product (III-70)
dppb	25	0	0	100
dppe	50	68	0	32
Dpe-Phos	97	56	23	21
Xantphos	82	32	49	19
P(o-tol) ₃	87	9	17	74
P(2-furyl)₃	97	71	7	21

^aConditions: 1.0 equiv amine, 1.2 equiv ArBr, 1.2 equiv NaOtBu, 1 mol % Pd₂(dba)₃, 8 mol % monodentate or 4 mol % bidentate ligands, toluene (0.2 M), 105 °C, 12h; reaction times have not been minimized.

Two experiments were performed to probe the origin of side products **III-69** and **III-70**. Resubjection of **III-70** to the reaction conditions did not result in the formation of **III-69** or **III-68** (eq 20). Furthermore, **III-68** was not converted to **III-69** when treated with 4-bromoanisole, NaOtBu, and catalytic Pd₂(dba)₃/P(2-fur)₃ (eq 21).



Scope of Carboamination Reactions for the Synthesis of 2,6-Disubstituted Piperazines

After achieving an efficient, flexible and straightforward route to the substrates and optimization of the key reaction, we set out to investigate the reaction scope. As shown in Table 10, the carboamination reactions are effective for transformations involving derivatives of several different amino acids including phenylalanine (**III-46**), valine (**III-47**), serine (**III-63**), alanine (**III-64**, **III-65**, **III-66**), and leucine (**III-67**). The reactions are tolerant of functionalized aryl groups on N1 (e.g., *p*-chlorophenyl and *p*-

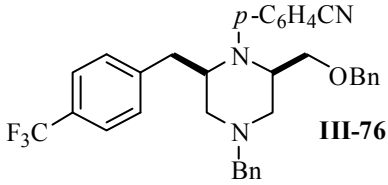
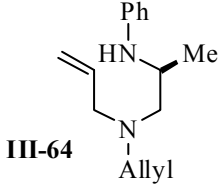
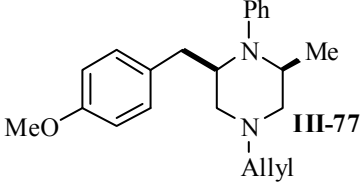
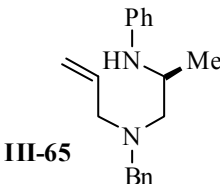
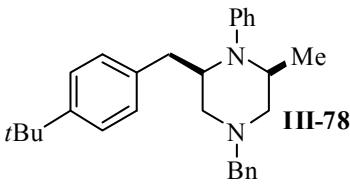
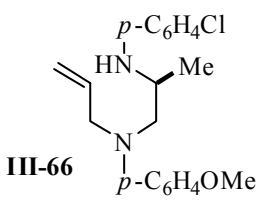
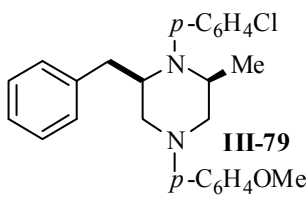
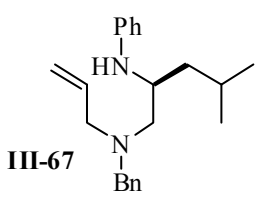
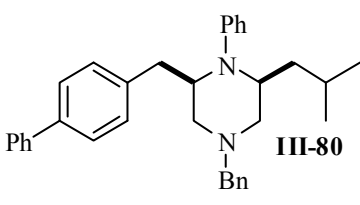
cyanophenyl) and several different protecting groups on N4 (e.g., benzyl, allyl, and *p*-methoxyphenyl).²⁶ Electron-rich, electron-neutral, and electron-poor aryl bromides can be employed as coupling partners, although use of β -bromostyrene provided low yields (ca. 25%) of the desired allylpiperazine derivative under these reaction conditions. In most cases the cyclizations afforded *cis*-2,6-disubstituted piperazines with >20:1 dr, although cyclizations of **III-63** proceed with slightly lower (14:1) diastereoselectivity.^{27,28} Interestingly, although the carboamination of N4-allyl substituted substrate **III-64** provided piperazine **III-77** with >20:1 dr (Entry 8), a related reaction of N4-benzyl-substituted substrate **III-65** provided piperazine **III-78** with only 9:1 dr (Entry 9).

Table 10. Synthesis of 2,6-Disubstituted Piperazines

Entry	Substrate	Product	dr	ee	Yield ^b
1	 III-46	 III-71	>20:1	99%	63%
2	III-46	 III-68	>20:1	99%	62%
3	III-46	 III-72	>20:1	98%	59%
4	 III-47	 III-73	>20:1	99%	51% ^c
5	III-47	 III-74	>20:1	99%	50%
6	 III-63	 III-75	14:1	97%	71%

^aConditions: 1.0 equiv amine, 1.2 equiv ArBr, 1.2 equiv NaOtBu, 1 mol % Pd₂(dba)₃, 8 mol % P(2-furyl)₃, toluene (0.2 M), 105 °C, 8–10 h; reaction times have not been minimized. ^bYields represent average isolated yields obtained from two or more experiments. ^cThe reaction was conducted using 2 mol % Pd₂(dba)₃ and 16 mol % P(2-furyl)₃.

Table 10 Continued.

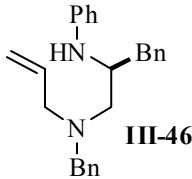
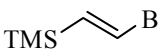
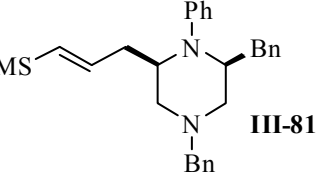
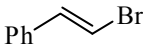
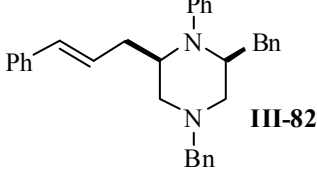
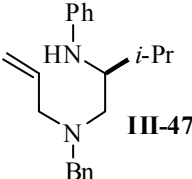

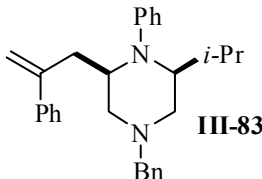
Entry	Substrate	Product	dr	ee	Yield ^b
7	III-63	 III-76	14:1	98%	69%
8	 III-64	 III-77	>20:1	99%	53%
9	 III-65	 III-78	9:1	---	54%
10	 III-66	 III-79	>20:1	99%	51%
11	 III-67	 III-80	>20:1	99%	57%

^aConditions: 1.0 equiv amine, 1.2 equiv ArBr, 1.2 equiv NaOtBu, 1 mol % Pd₂(dba)₃, 8 mol % P(2-furyl)₃, toluene (0.2 M), 105 °C, 8–10 h; reaction times have not been minimized. ^bYields represent average isolated yields obtained from two or more experiments. ^cThe reaction was conducted using 2 mol % Pd₂(dba)₃ and 16 mol % P(2-furyl)₃.

Reactions with vinyl halide electrophiles were also feasible in Pd-catalyzed carboamination reactions for the synthesis of substituted piperazines **III-81-III-83**. Use of a slightly higher catalyst loading (2 mol % Pd₂(dba)₃/4 mol % Pd) was necessary to

achieve complete consumption of starting material in these transformations. As shown in Table 11, formation of the desired piperazines occurred with high diastereoselectivity and excellent enantiopurity.

Table 11. Carboamination Reaction of δ -Amino Olefins with Vinyl Halides^a

Entry	Substrate	Vinyl-X	Product	dr	ee	Yield
1				>20:1 dr	97%	58% ^a
2				>20:1 dr	95%	70% ^a
3				>20:1 dr	97%	50% ^b

^aConditions: 1.0 equiv amine, 1.4 equiv ArBr, 1.4 equiv NaOtBu, 2 mol % Pd₂(dba)₃, 16 mol % P(2-furyl)₃, toluene (0.2 M), 90 °C, 12-15h; The reaction times have not been minimized. ^bThis reaction was performed with xylenes in place of toluene at 135 °C.

The cyclization of Boc-protected amines **III-55** and **III-57** was also investigated. It was found that a catalyst composed of Pd(OAc)₂/P(2-fur)₃ and a reaction temperature of 90 °C provided optimal yields of the desired piperazine products. In contrast to cyclizations of Boc-amines to afford piperidines (Chapter II), in which Boc-decomposition was a severe limitation, this was not an issue in the analogous Boc-protected piperazine-forming reactions. The reactions proceeded in good yields to

provide the desired piperazine products **III-84** and **III-85**. However, diastereoselectivities in the reactions were low (1 to 2:1 dr).

Table 12. Carboamination Reaction of δ -*N*-Boc-Protected Amino Olefins with 4-Br-Benzonitrile^a

Entry	Substrate	Product	dr	ee	Yield
1			1:1 dr	99% ^b	68%
2			2:1 dr	--	63%

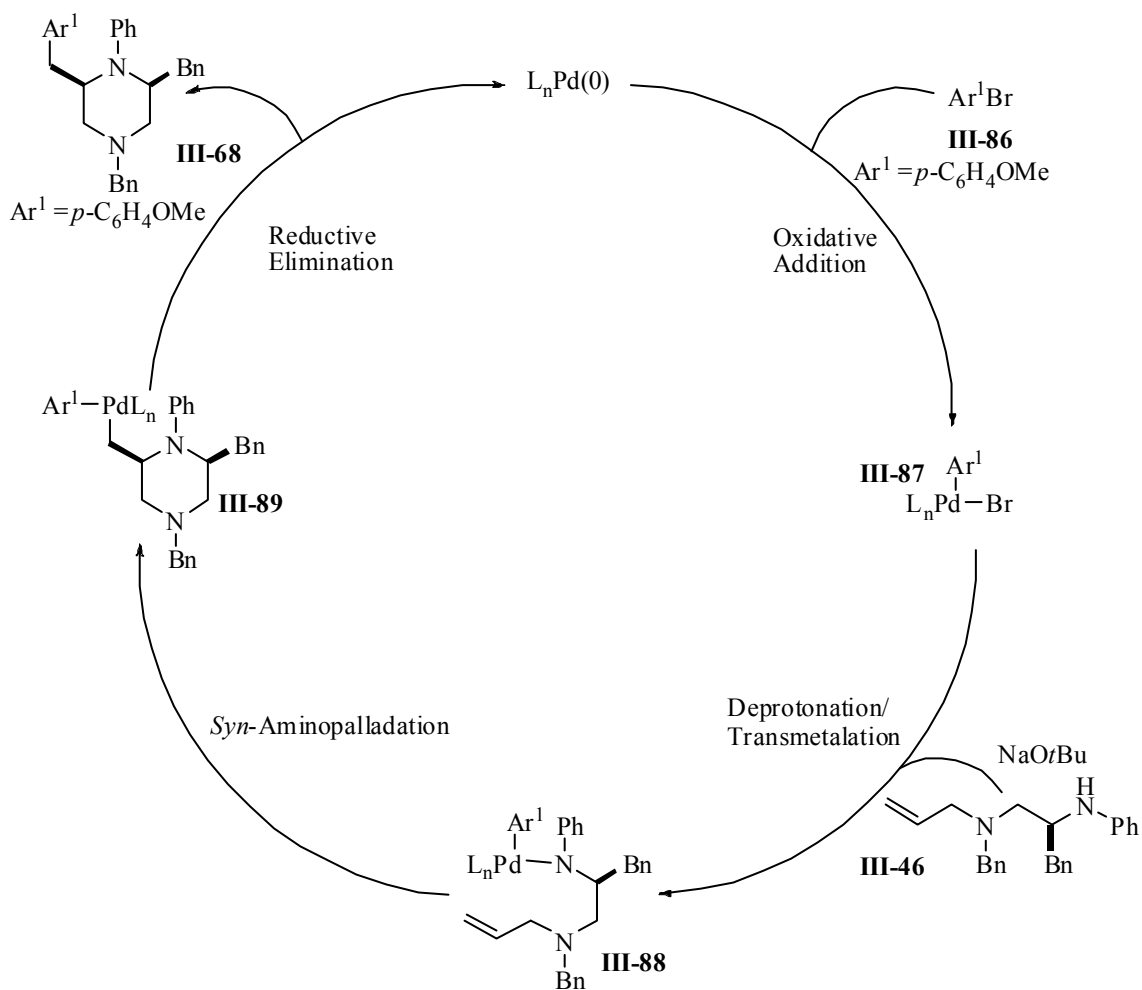
^aConditions: 1.0 equiv amine, 1.2 equiv ArBr, 1.2 equiv NaOtBu, 6 mol % Pd(OAc)₂, 8 mol % P(2-fur)₃, toluene (0.2 M), 90 °C, 3-12h; the reaction times have not been minimized.^b The enantiopurity of each diastereomer was measured to be 99%.

Mechanism of Carboamination Reaction for the Synthesis of 2,6-Disubstituted Piperazines

A plausible mechanism for the Pd-catalyzed piperazine forming reactions is shown below (Scheme 27). These transformations appear to be mechanistically analogous to previously described carboamination reactions of γ -aminoalkenes with aryl bromides, and are likely initiated by oxidative addition of the aryl bromide to Pd(0) to generate **III-87**.

This intermediate can react with the amine and NaOtBu to provide a palladium (aryl)(amido) complex **III-88**, which can undergo syn-aminopalladation^{13a,d} to afford **III-89**. Carbon-carbon bond-forming reductive elimination would then yield the observed piperazine product **III-68**.

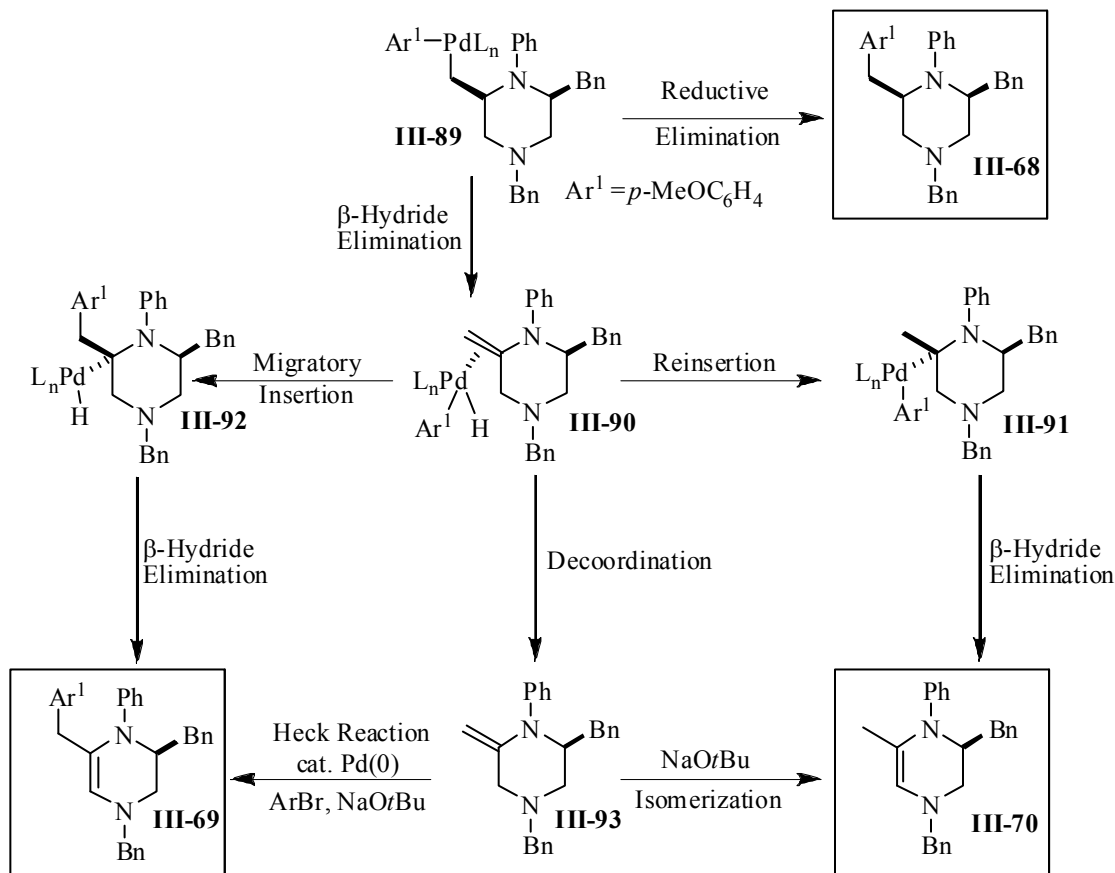
Scheme 27. Proposed Catalytic Cycle for Piperazine Formation



Side products **III-69** and **III-70** most likely derive from a common intermediate (**III-90**) which results from competing β -hydride elimination of **III-89** (Scheme 28). The intermediate **III-90** was never detected in the *N*-aryl piperazine-forming reaction, but the

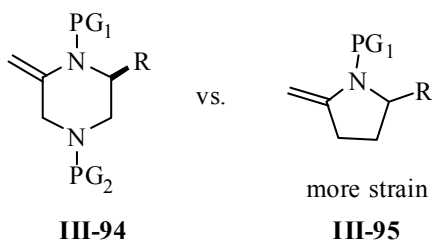
analogous intermediate was isolated in the *N*-Boc piperazine-forming reaction as the major side product (Boc in place of aryl-protected nitrogen). Compound **III-70** could be generated by insertion of the alkene into the Pd–H bond of **III-90** followed by β -hydride elimination from the C5 position of **III-91**. Alternatively, displacement of Pd from **III-90** would afford **III-93**, which could be converted to the more thermodynamically stable derivative **III-70** by reaction with NaOtBu. Side product **III-69** most likely results from Heck-type arylation of **III-93**, although formation of **III-69** via carbopalladation of **III-90** followed by C5 β -hydride elimination from **III-92** cannot be ruled out.²⁹ The generation of **III-69** and **III-70** provides further evidence to support the mechanism of 2,6-disubstituted piperazine formation shown above, rather than a mechanism involving alkene carbopalladation of **III-88**.^{13a,d}

Scheme 28. Origin of Side Products in Piperazine-Forming Reactions



Interestingly, the production of undesired compounds resulting from β -hydride elimination of **III-89** is more problematic in the *N*-aryl-piperazine-forming reactions than the analogous *N*-aryl-pyrrolidine-forming reactions.^{13a,30} This may be due to the fact that the transition state for β -hydride elimination from the five-membered pyrrolidine ring to form *exo*-olefin **III-95** is more strained (due to rehybridization of the C2-carbon from sp^3 to sp^2) than the analogous transition state for conversion of the six-membered ring **III-89** to **III-94**.

Figure 4. Comparison of β -hydride Elimination Products in Six- Vs. Five-Membered Rings

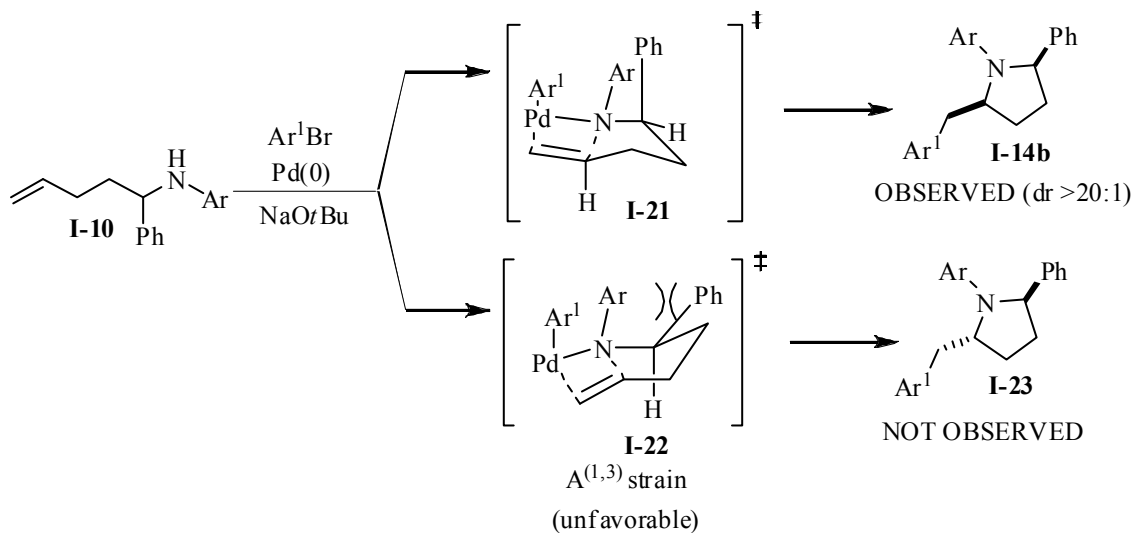


The piperazine-forming reactions are significantly better reactions than the piperidine-forming reactions described in Chapter II. The nitrogen in the tether of the piperazine substrate appears to facilitate the six-membered ring forming reaction and likely assists in bringing the two ends of the molecule together, thereby combating the entropic challenges associated with cyclizing δ -amino olefins to piperidines.

Stereochemical Discussion on Carboamination Reaction for the Synthesis of 2,6-Disubstituted Piperazines

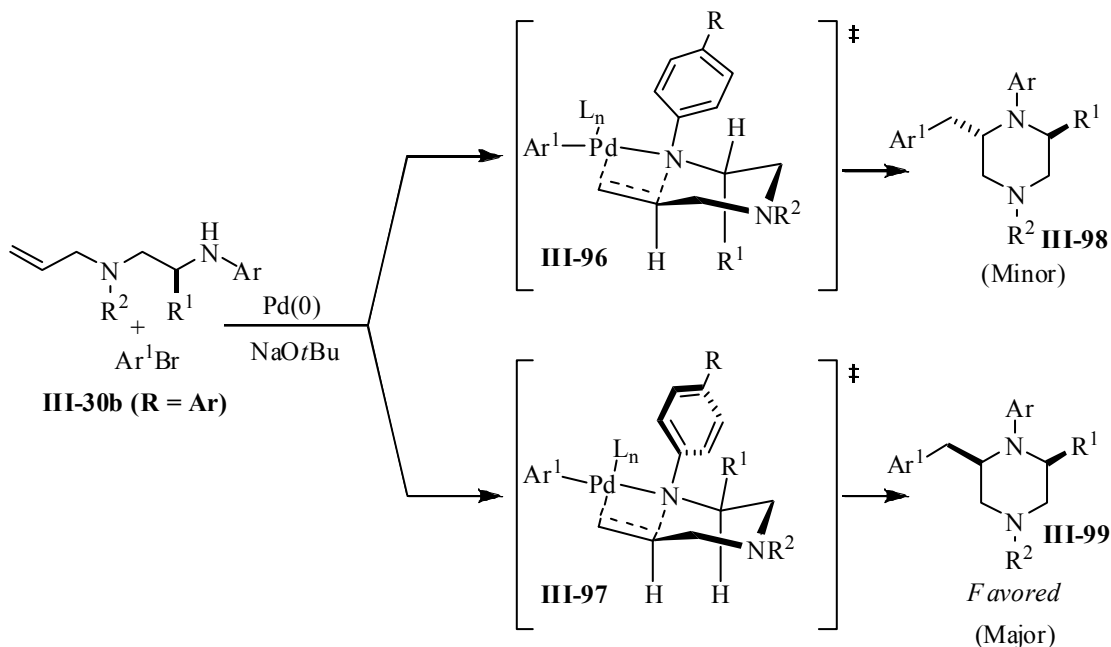
The stereochemical outcome of the piperazine-forming reactions contrasts with our model for the analogous pyrrolidine-forming reactions, which are believed to proceed via a transition state in which the C1-substituent is placed in a pseudoaxial orientation to minimize A^(1,3) strain between the C1-group and the N-substituent (Ar, Boc, or Cbz) as shown below (Scheme 29).^{13a,g,j}

Scheme 29. Explanation of Stereochemistry for 2,5-*Cis*-Disubstituted Pyrrolidine-Forming Carboamination Reactions

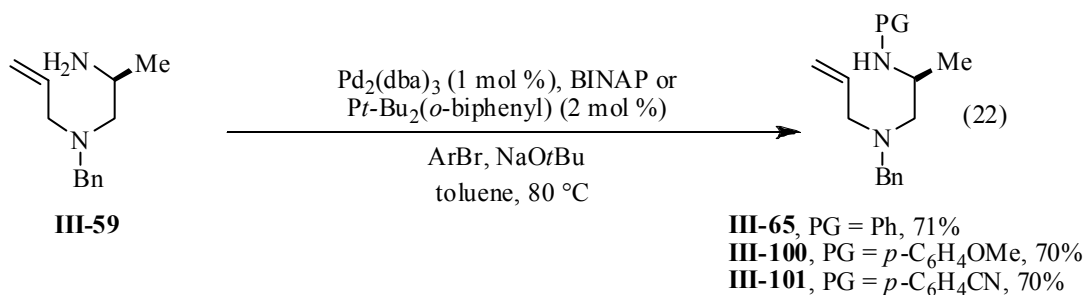


A similar transition state structure (**III-96**) should afford *trans*-2,6-disubstituted piperazines (Scheme 30), which are not the major products in these reactions. Therefore, we needed to establish a new model for the carboamination of diamines to provide substituted piperazines. Our current working hypothesis for piperazine formation involves cyclization via transition state **III-97**, in which the N1-Ar group is rotated such that N1 is pyramidalized. This conformational change eliminates the $A^{(1,3)}$ strain interaction when the α -substituent (R1) is oriented in a pseudoequatorial position, and thereby leads to the *cis*-2,6-disubstituted stereoisomers. This hypothesis is consistent with the observation that cyclizations of substrates bearing N1-(*p*-cyanophenyl) or N1-Boc groups, which should have a decreased degree of N1-pyramidalization, proceed with lower diastereoselectivity.^{28,31}

Scheme 30. Explanation of Stereochemistry for 2,6-*Cis*-Disubstituted Piperazine-Forming Carboamination Reactions

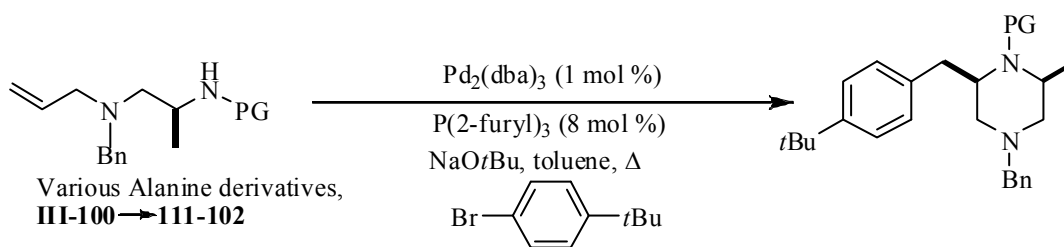


In order to further probe this hypothesis, we devised an experiment in which we prepared various differentially aryl-protected alanine derivatives and subjected them to the optimized reaction conditions (Table 13). Alanine derivatives bearing a benzyl group on N4 were chosen because the diastereoselectivity was occasionally lower than 20:1 dr with this substrate (Table 10, Entry 9). The substrates were prepared as discussed in Scheme 26 using intermediate **III-59** with the appropriate aryl halide as shown in eq 22.



We found the most electron-donating *N*-aryl protecting group (*p*-methoxyphenyl) provides excellent diastereoselectivity for the *cis*-diastereomer (**III-99**) and is therefore more likely to react via transition state **III-97**. In contrast, more delocalized systems may have a greater tendency to cyclize via transition state **III-96**, although this still appears to be a relatively high energy pathway. These results are consistent with our hypothesis, as the N1-lone pair delocalization should be decreased with a more electron rich protecting group such as *p*-methoxyphenyl. The phenyl-substituted substrate **III-65** provides lower diastereoselectivity (**III-78**) and *N*-*p*-cyanophenyl, the most e-poor of the aromatic systems investigated, generates the product with 6:1 dr (**III-103**). Attempts to cyclize a *p*-nitrophenyl substituted substrate led to decomposition of the substrate. Finally, use of a Boc protecting group, provides the product with 1:1 diastereoselectivity (**III-104**) and in modest yield.^{32,33}

Table 13. Dependence of Diastereoselectivity on N1-Protecting Group



PG	Diastereoselectivity	Isolated Yield (Piperazine)
PMP (III-100)	>20:1	45% (III-102)
Ph (III-65)	9:1	54% (III-78)
<i>p</i> -C ₆ H ₄ CN (III-101)	6:1	74% (III-103)
Boc (III-55)	1:1	8% (III-104)

The effect of the N4-protecting group on stereochemistry was also briefly examined (Table 14). Substrates **III-64** and **III-65** were examined (prepared as discussed in Scheme 26) as well as substrate **III-105**, which was prepared via *N*-arylation (eq 23) with bromobenzene of intermediate **III-61** from Scheme 26. The nature of the N4-protecting group also has a subtle effect on the diastereoselectivity, but the reasons for this are not entirely clear (Table 14).³⁴

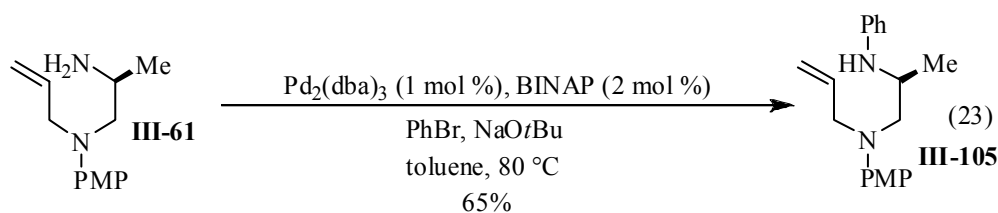
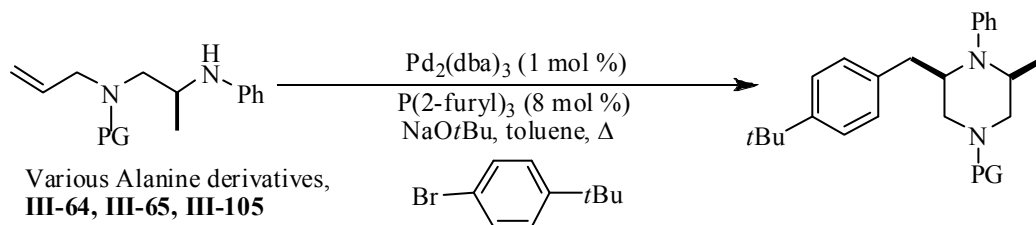


Table 14. N4-Protecting Group Diastereoselectivity Study

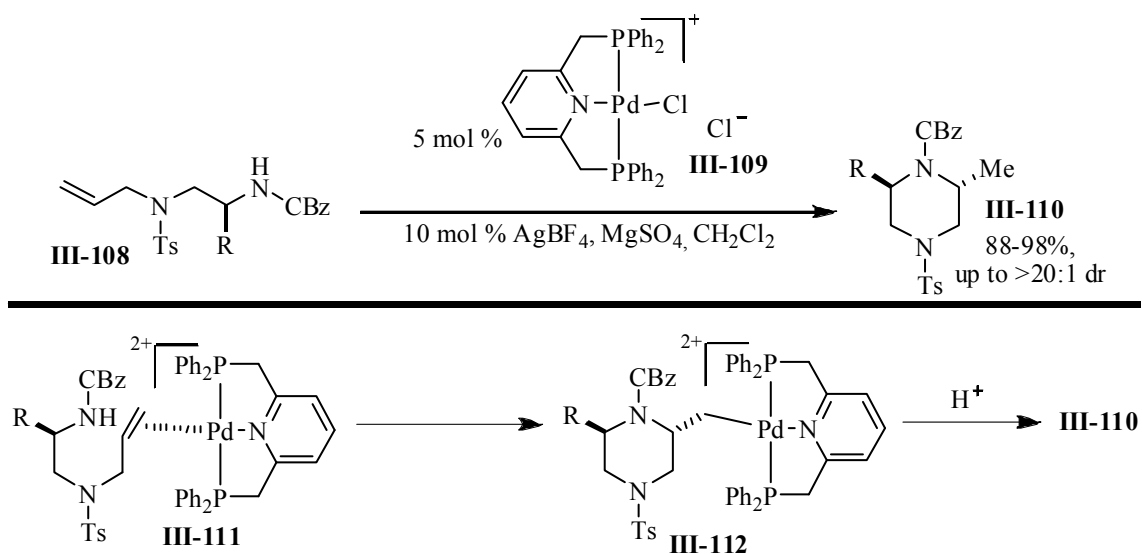


PG	Diastereoselectivity	Isolated Yield (Piperazine)
Bn (III-65)	9:1	54% (III-78)
Allyl (III-64)	>20:1	45% (III-106)
PMP (III-105)	>20:1	50% (III-107)

After our preliminary communication on the synthesis of substituted *cis*-2,6-disubstituted piperazines,¹ Michael and coworkers³⁵ reported a complementary method for the synthesis of *trans*-2,6-disubstituted piperazines via Pd-catalyzed hydroamination

reactions (Scheme 31). The Pd-activated olefin is attacked by the nucleophilic amine as shown in **III-111** which is followed by protonolysis of **III-112** to release the product. However, this transformation is limited to the preparation of compounds bearing a methyl group in the 2-position. The authors propose an allylic strain argument³⁶ to explain the formation of the 2,6-*trans* disubstituted piperazine whereby the α -substituent orients itself in the pseudo-axial position in order to avoid $A^{(1,3)}$ strain in the transition state. The tridentate Pd-catalyst is believed to inhibit β -hydride elimination of the intermediate Pd-alkyl species **III-112**.

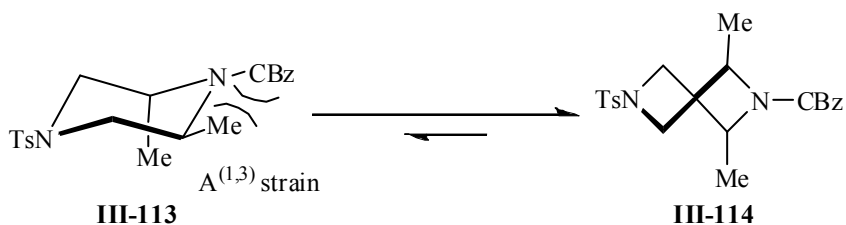
Scheme 31. Synthesis of 2,6-Disubstituted Piperazines Via Hydroamination



The *trans* stereochemistry of the products was determined by X-ray crystal structure analysis and it was found that the piperazine ring exists in the twist boat conformation. While the molecule adopts a chair conformation for cyclization, the twist boat conformation is preferred after cyclization because of an unfavorable $A^{(1,3)}$

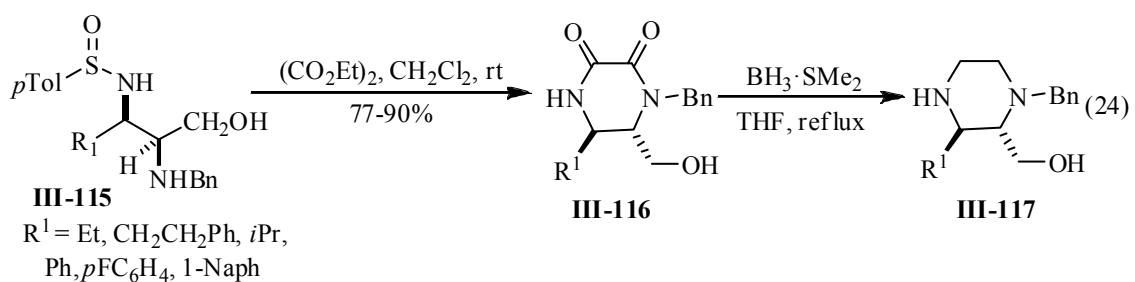
interaction between the CBz-group and the methyl group if it were to remain in the equatorial position (Figure 4). Though the half-chair is high in energy, the authors argue it may be favorable because of the presence of the two nitrogen atoms in the ring which would likely reduce the torsional strain of the molecule.

Figure 5. Proposed Twist Boat Conformation for Hydroamination Reactions

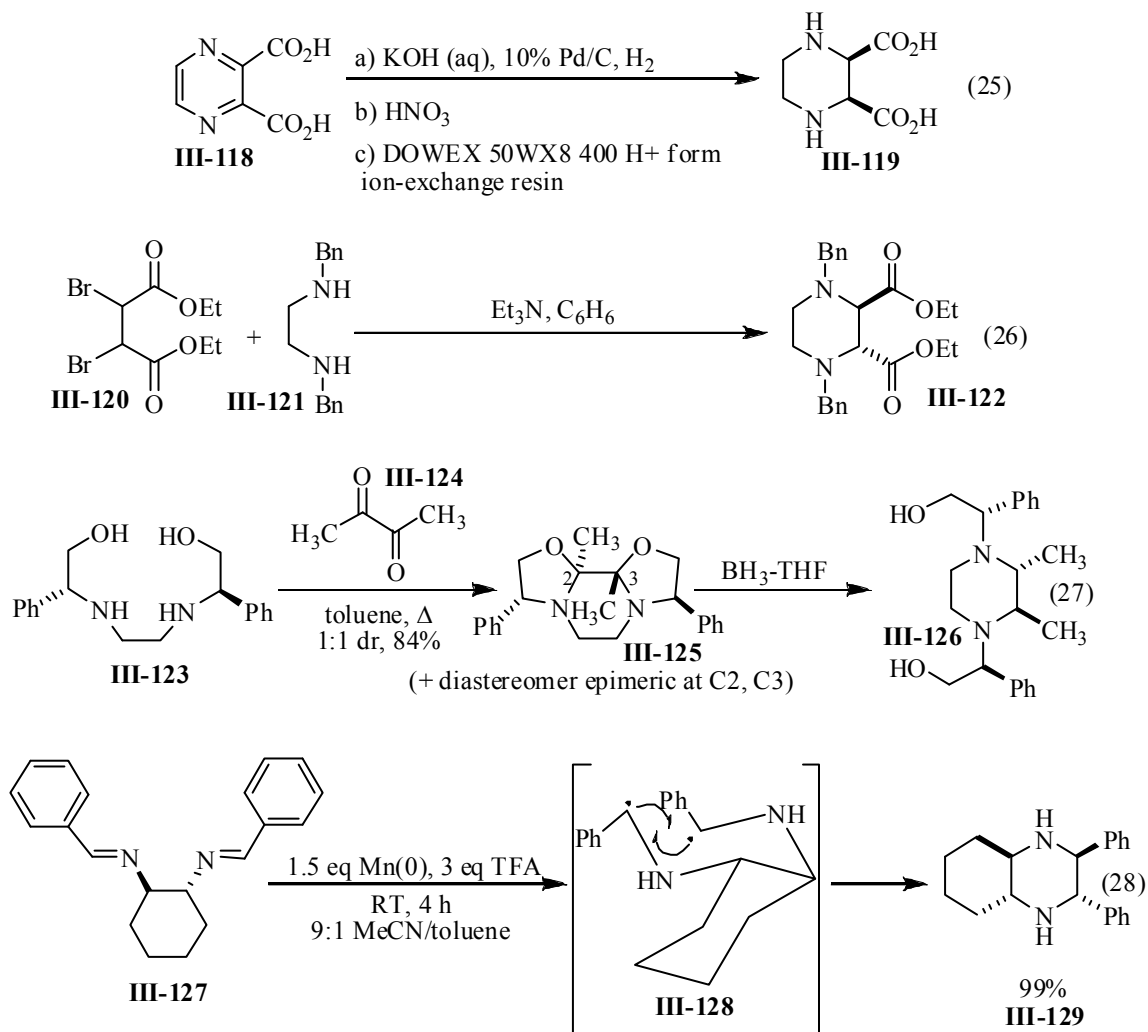


Background: Carboamination Reaction for the Synthesis of 2,3-Disubstituted Piperazines

The synthesis of non-symmetrical 2,3-disubstituted piperazines is also limited in scope. Common methods involve reduction of 2,3-diketopiperazines (eq 24).³⁷ However, the synthesis of unsymmetrical substituted diketopiperazines relies on the availability of enantiopure differentially substituted vicinal diamines,³⁸ which are difficult to prepare.



Other methods for the synthesis of 2,3-disubstituted piperazines involve reduction of the corresponding pyrazine (eq 25),³⁹ substitution of a suitably substituted alkyl halide (eq 26),⁴⁰ via reductive amination (eq 27),⁴¹ and via a Bronsted acid/Mn(0) mediated radical cyclization reaction (eq 28).⁴²

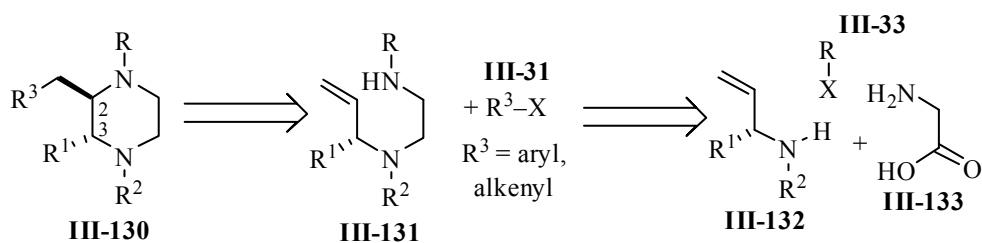


Substrate Synthesis

We next elected to examine the Pd-catalyzed carboamination reaction for the synthesis of 2,3-disubstituted piperazines. As shown in the retrosynthesis in Scheme 32

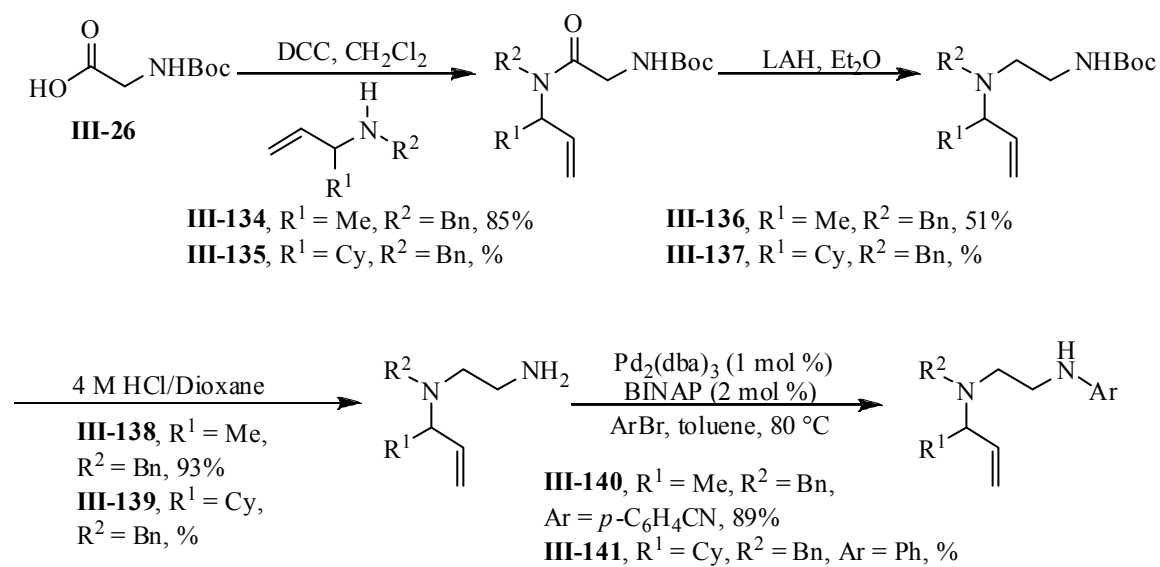
below, our approach relies on access to α -substituted allylic amines, which could be coupled with glycine and reduced to afford the diamine derivative **III-131**.

Scheme 32. Retrosynthetic Analysis for 2,3-Disubstituted Piperazines

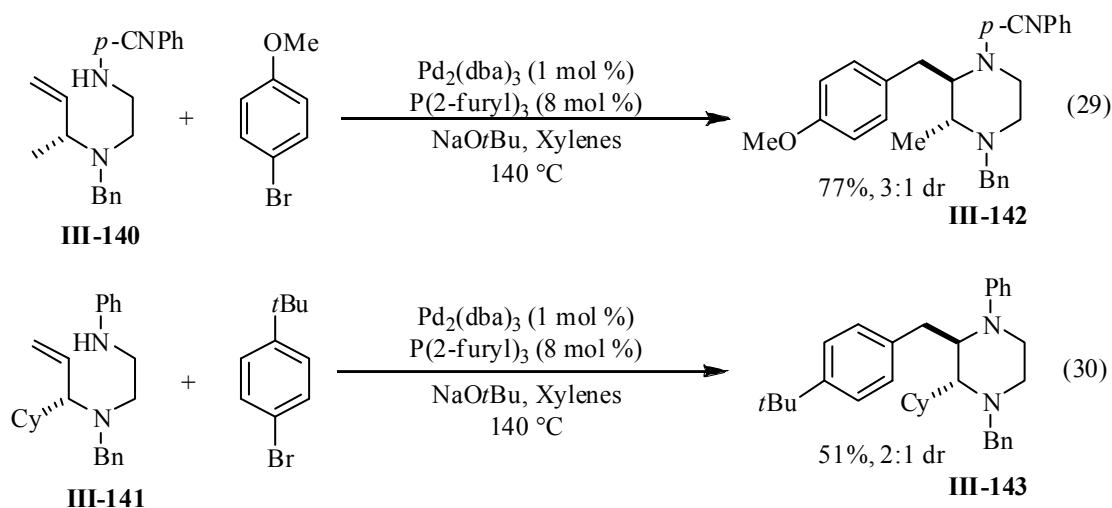


The substrates for these reactions were prepared in four steps via amide coupling of Boc-glycine (**III-26**) and readily available α -substituted allylic amines.⁴³ Reduction of the resulting amide, followed by cleavage of the Boc-group, and *N*-arylation provided substrates **III-140** and **III-141**.

Scheme 33. Synthesis of Substrates for 2,3-Disubstituted Piperazine Synthesis

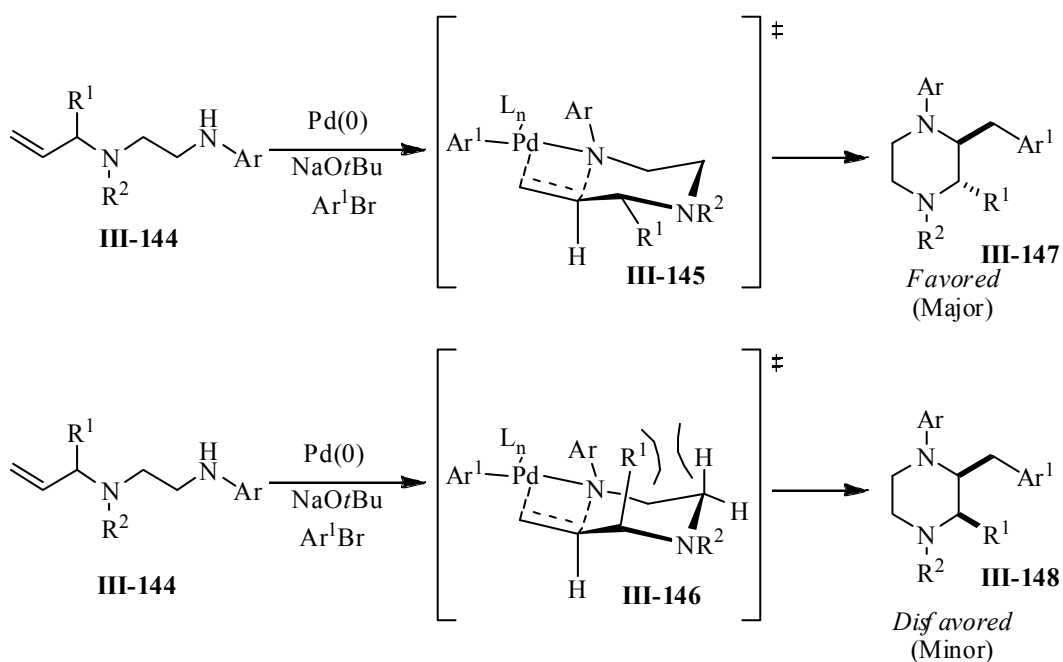


The Pd-catalyzed carboamination reactions of **III-140** and **III-141** were then examined using the reaction conditions optimized for the synthesis of 2,6-disubstituted piperazines. These conditions required slight modification as it was necessary to employ higher temperatures (xylenes, 140 °C) in order to effect consumption of starting material. The reactions (eq 29 and eq 30)⁴⁴ proceed with good to moderate yields and modest levels of diastereoselectivity.



The major diastereomer observed in the 2,3-disubstituted piperazine cyclizations (eq 29 and eq 30) is the *trans*-diastereomer. The modest stereocontrol likely results from equatorial or axial positioning of the allylic substituent in the transition state as shown in Scheme 34. The minor diastereomer is less favored due to unfavorable 1,3-diaxial interactions. These reactions required more forcing conditions in order that they may go to completion and were therefore conducted in xylenes at 140 °C.

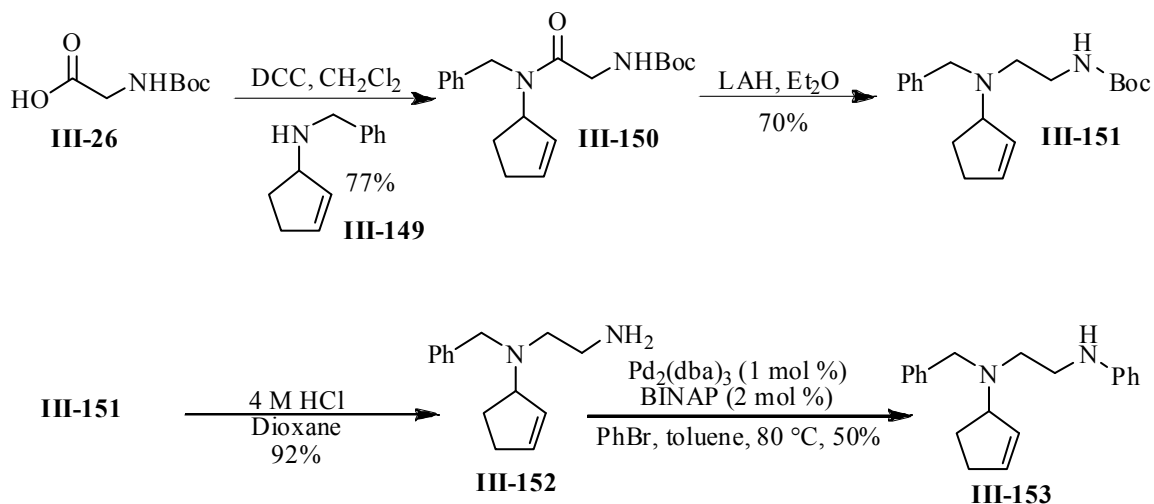
Scheme 34. Explanation of Stereochemistry for 2,3-*Trans*-Disubstituted Piperazine-Forming Carboamination Reactions



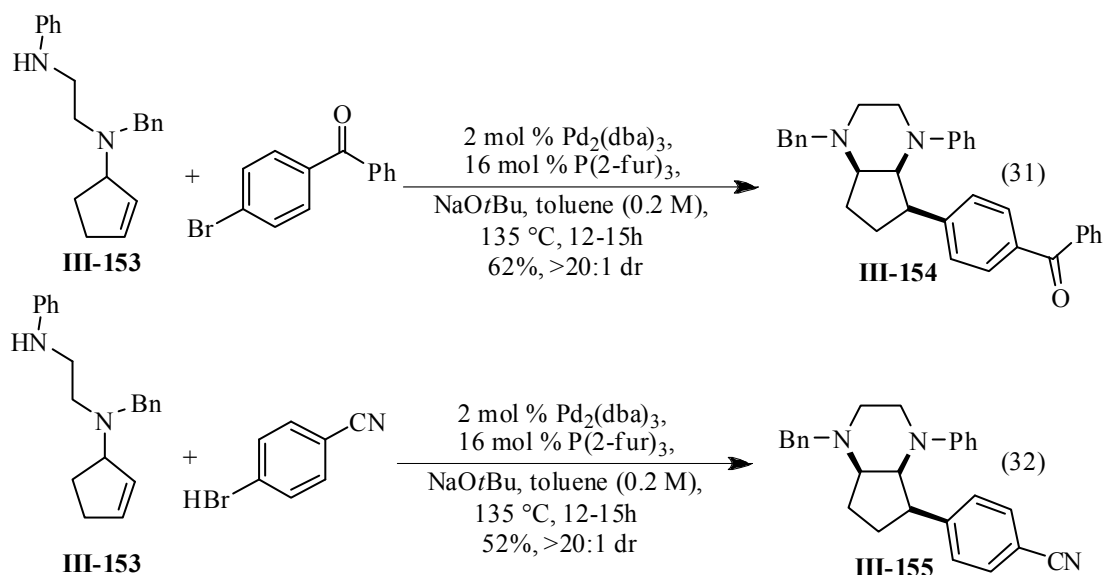
Carboamination Reaction of Cyclic Amines for the Synthesis of Bicyclic Piperazines

In order to generate structurally rigid piperazine scaffolds, we also investigated carboaminations of cyclic internal olefin substrate (**III-153**). This substrate was prepared by treatment of *N*-benzylcyclopent-2-enamine (**III-149**) (prepared in one step from hydroamination of cyclopentadiene)⁴⁵ with Boc-protected glycine **III-26**. The resulting amide was reduced to provide amine **III-151**. Boc-protected amine **III-151** did not undergo the carboamination reaction under various reaction conditions screened. Therefore, **III-151** was deprotected with 4M HCl/dioxane to afford primary amine **III-152**, which was subsequently *N*-arylated with bromobenzene to afford **III-153**.

Scheme 35. Synthesis of Cyclic Olefin Substrate **III-153**



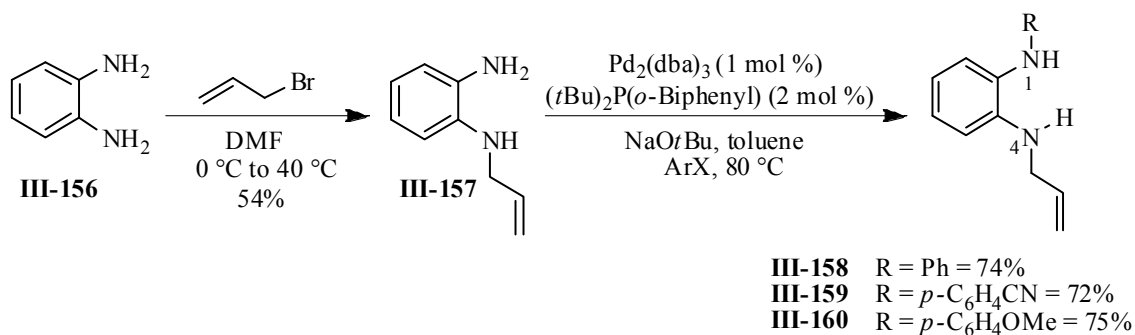
Under optimized reaction conditions (2 mol % $\text{Pd}_2(\text{dba})_3$: 16 mol % $\text{P}(\text{2-fur})_3$), substrate **III-153** was converted to **III-154** and **III-155** in good yield and with excellent diastereocontrol (eq 31 and 32). A NOESY-2D experiment revealed the stereochemical outcome of the transformation to be syn-addition across the olefin, which provides additional evidence for the syn-amino-palladation mechanism proposed in Scheme 27. Side products in these reactions originate from π -allyl formation and consequently loss of the diamine component of the starting material **III-153**.



Carboamination Reaction for the Synthesis of Benzopiperazines

We have also briefly examined the synthesis of benzopiperazines using the Pd-catalyzed carboamination reaction. The substrates for these reactions were prepared via *N*-arylation of *N*-allyl phenylenediamines **III-157** as shown in Scheme 36, which in turn were prepared via allylation of 1,2-diaminobenzene.⁴⁶

Scheme 36. Synthesis of Phenylene-Diamine Substrates

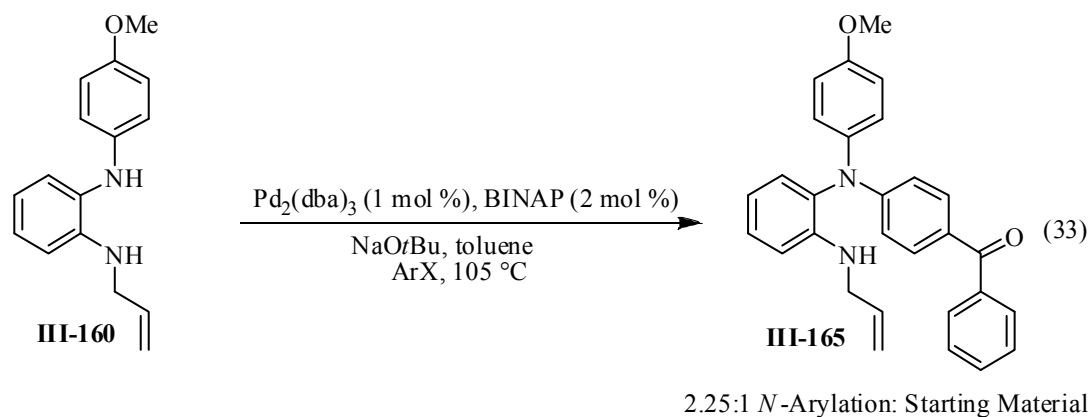


Treatment of these substrates with an aryl bromide and NaOtBu and a catalyst system composed of Pd₂(dba)₃/BINAP afforded benzopiperazines **III-161-III-164** with N4 unprotected. In cases where an electron-poor aryl halide was used, *N*-arylation of N1 was a competing side reaction (eq 33) as evidenced by isolation and ¹H-¹H COSY analysis of this side product (**III-165**).⁴⁷ Use of P(2-fur)₃ as the ligand did not provide any of the piperazine product, and only unreacted starting material was observed in the crude reaction mixture.

Table 15. Synthesis of Benzopiperazines^a

Entry	Substrate	Product	Yield
	<p style="text-align: center;"> $\text{Pd}_2(\text{dba})_3, \text{BINAP}$ NaOtBu, toluene $\text{ArX, 105 } ^\circ\text{C}$ </p>		
1	<p style="text-align: center;">III-158</p>	<p style="text-align: center;">III-161</p>	62%
2	<p style="text-align: center;">III-159</p>	<p style="text-align: center;">III-162</p>	60%
3	<p style="text-align: center;">III-159</p>	<p style="text-align: center;">III-163</p>	63%
4	<p style="text-align: center;">III-160</p>	<p style="text-align: center;">III-164</p>	48%

^aConditions: 1.0 equiv amine, 1.0 equiv ArBr, 1.2 equiv NaOtBu, 1 mol % Pd₂(dba)₃, 2 mol % BINAP, toluene (0.2 M), 105 °C, 10h; the reaction times have not been minimized.



Conclusion

In conclusion, we have developed a new method for the synthesis of substituted piperazines, including 2,6-disubstituted aryl protected piperazines, Boc-protected disubstituted piperazines, 2,3-disubstituted piperazines, benzopiperazines, and bicyclic piperazines. In cases where 2,6-disubstituted piperazines are prepared, our strategy allows for the modular construction of a number of derivatives containing different substituents at C2, C6, N1, and N4 from simple starting materials with excellent stereoselectivity.

Experimental Section

General Considerations: All reactions were carried out under an argon or nitrogen atmosphere in oven- or flame-dried glassware. All catalysts, reagents, and aryl bromides were obtained from commercial sources and were used without further purification. *N*-phenyl-L-phenylalanine and *N*-phenyl-L-valine were prepared according to published procedures.¹⁶ DEPBT was prepared according to the procedure of Goodman¹⁸ and was purified by recrystallization from petroleum ether:ethyl acetate (1:1) followed by trituration with ethyl acetate to yield a white solid. Use of pure, colorless, reagent was essential to prevent degradation of enantiomeric purity during amide bond formation. Toluene, THF, ether, and dichloromethane were dried and purified using a GlassContour solvent purification system. Structural and stereochemical assignments were made on the basis of 2-D COSY, HSQC, and NOESY experiments. Ratios of diastereomers were determined by ¹H NMR and/or capillary GC analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be $\geq 95\%$ pure as determined by ¹H NMR, GC, and/or combustion analysis. The yields reported in the experimental section describe the result of a single experiment, whereas the yields reported in Tables 9-15, Schemes 21–23, 25, 26, 33, 35-36, and eq 13, 22, 23, 29-32 are average yields of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in Tables 9–15, Schemes 21–23, 25, 26, 33, 35-36, and eq 13, 22, 23, 29-32.

***N,N*-diallyl-2-(phenylamino)acetamide (III-21).** A flame-dried round-bottomed flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the *N*-phenyl amino acid substrate (1.32 g, 8.73 mmol).⁴⁸ THF was added to provide a 0.3

M solution, which was cooled to 0 °C and stirred. CDI (1.42 g, 8.73 mmol) was added, followed immediately by 881 mg diallylamine (1.12 mL, 9.07 mmol), and the resulting reaction mixture was stirred for 12 h at room temperature. Aqueous sodium bicarbonate was then added at room temperature, and the resulting reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified via flash chromatography on silica gel to provide 1.31 g (65%) of the title compound as a yellow oil and a 1:1 mixture of rotamers. ¹H NMR (400 MHz, CDCl₃) δ 7.22–7.18 (m, 2 H), 6.73 (tt, *J* = 0.8, 7.2 Hz, 1 H), 6.62 (dd, *J* = 1.2, 8.8 Hz, 2 H), 5.85–5.74 (m, 2 H), 5.28–5.21 (m, 2 H), 5.20–5.15 (m, 2 H), 4.88 (s, 1 H), 4.07 (d, *J* = 6 Hz, 2 H), 3.90–3.89 (m, 4 H); ¹³C NMR (100 MHz, CDCl₃) δ 169.2, 147.5, 132.8, 132.2, 129.4, 118.0, 117.6, 117.4, 113.1, 48.5, 48.3, 45.2; IR (film) 3387, 2919, 1655 cm⁻¹. Anal calcd for C₁₄H₁₈N₂O: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.98; H, 7.87; N, 12.07.

***N*¹, *N*¹-diallyl- *N*²-phenylethane-1,2-diamine (III-22).** A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the *N,N*-diallyl-2-(phenylamino)acetamide (III-21) substrate (1.01 g, 4.39 mmol). Diethyl ether was added to provide a 0.5 M solution, which was cooled to 0 °C with stirring. A solution of lithium aluminum hydride in diethyl ether (9.65 mL, 1 M in diethyl ether, 2.2 equiv) was added dropwise, and the resulting mixture was stirred at 0 °C until the starting amide was completely consumed as judged by TLC analysis (8 h). Water (2 mL) was added dropwise, followed by 10 M aqueous NaOH (5 mL), and additional water (2 mL). The resulting suspension was stirred at rt for 5–10 minutes, then decanted, dried over

anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 805 mg (85%) of the title compound as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.20–7.16 (m, 2 H), 6.70 (t, $J = 7.2$ Hz, 1 H), 6.62 (dd, $J = 1.2, 8.8$ Hz, 2 H), 5.90–5.80 (m, 2 H), 5.21–5.13 (m, 4 H), 4.26 (s, 1 H), 3.16–3.12 (m, 6 H), 2.72 (t, $J = 6.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.7, 135.5, 129.3, 117.8, 117.3, 113.1, 56.7, 51.8, 41.2; IR (film) 3379, 2811, 1602 cm^{-1} . Anal calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.50; H, 9.32; N, 13.02.

Synthesis of Piperazines via Coupling with Aryl Bromides (eq 23-25)

General Procedure for Pd-Catalyzed Synthesis of *N*-Aryl Monosubstituted Piperazines. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with $\text{Pd}_2(\text{dba})_3$ (1 mol % complex, 2 mol % Pd), dppb (2 mol %), sodium *tert*-butoxide (1.2 equiv), and the aryl bromide (1.2 equiv). In some cases, 4 mol % of $\text{P}(2\text{-furyl})_3$ was employed as the ligand is used and this is stated in the relevant examples. The Schlenk tube was purged with nitrogen and the amine was added as a solution in toluene (2.5 mL/0.5 mmol substrate). The Schlenk tube was then heated to 105 °C with stirring until the starting material has been consumed as judged by ^1H NMR analysis of an aliquot taken from the reaction mixture. The reaction mixture was then cooled to room temperature, saturated aqueous ammonium chloride (2–3 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and

concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

4-allyl-2-(4-*tert*-butylbenzyl)-1-phenylpiperazine (III-23). The reaction of 100 mg (0.462 mmol) of *N*¹,*N*¹-diallyl-*N*²-phenylethane-1,2-diamine (**III-22**) with 118.2 mg (96.2 μ l, 0.554 mmol) of 4-bromo-*tert*-butylbenzene was conducted for 10 h according to the general procedure using dppb as the ligand (2 mol %). Upon purification, 120 mg (74%) of the title compound was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.33 (m, 4 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 8 Hz, 2 H), 6.89 (t, *J* = 7.2 Hz, 1 H), 6.03–5.93 (m, 1 H), 5.27–5.19 (m, 2 H), 3.98–3.94 (m, 1 H), 3.39 (dt, *J* = 2.8, 11.6 Hz, 1 H), 3.31–3.25 (m, 1 H), 3.20–3.11 (m, 2 H), 3.03–2.95 (m, 2 H), 2.88 (dt, *J* = 2.4, 9.2 Hz, 1 H), 2.60 (dd, *J* = 2.8, 12.8 Hz, 1 H), 2.32 (td, *J* = 3.6, 11.2 Hz, 1 H), 2.16 (dd, *J* = 3.2, 11.6 Hz, 1 H), 1.34 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 149.9, 148.9, 137.2, 135.4, 129.5, 129.2, 125.4, 119.0, 118.0, 115.9, 61.9, 58.2, 54.0, 53.6, 43.6, 34.5, 32.1, 31.6; IR (film) 2960, 1598 cm⁻¹. Anal calcd for C₂₄H₃₂N₂: C, 82.71; H, 9.25; N, 8.04. Found: C, 82.72; H, 9.32; N, 8.01.

4-allyl-1-phenyl-2-(pyridin-3-ylmethyl)piperazine (III-24). The reaction of 100 mg (0.462 mmol) of *N*¹, *N*¹-diallyl-*N*²-phenylethane-1,2-diamine (**III-22**) with 73 mg (54.4 μ l, 0.554 mmol) of 3-bromo-pyridine was conducted for 10 h according to the general procedure using dppb as the ligand (2 mol %). Upon purification, 90 mg (66 %) of the title compound was obtained as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 8.44–8.42 (m, 2 H), 7.44 (d, *J* = 7.5 Hz, 1 H), 7.31 (t, *J* = 7 Hz, 2 H), 7.20–7.17 (m, 1 H), 6.96 (d, *J*

= 9 Hz, 2 H), 6.86 (dt, $J = 1, 7.5$ Hz, 1 H), 5.93–5.85 (m, 1 H), 5.21–5.15 (m, 2 H), 3.93–3.90 (m, 1 H), 3.34 (dt, $J = 3.5, 12$ Hz, 1 H), 3.27–3.22 (m, 1 H), 3.18–3.13 (m, 1 H), 3.11–3.07 (m, 1 H), 2.99–2.96 (m, 1 H), 2.92–2.88 (m, 1 H), 2.71 (dt, $J = 2, 11.5$ Hz, 1 H), 2.59 (dd, $J = 3, 12.5$ Hz, 1 H), 2.29 (td, $J = 3.5, 11$ Hz, 1 H), 2.14 (dd, $J = 3.2, 11.5$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.9, 149.8, 147.7, 136.8, 135.7, 135.1, 129.6, 123.5, 119.5, 118.3, 116.2, 61.9, 58.3, 53.7, 53.5, 43.6, 29.9; IR (film) 3392, 2948, 2801, 1597 cm^{-1} . Anal calcd for $\text{C}_{19}\text{H}_{23}\text{N}_3$: C, 77.78; H, 7.90; N, 14.32. Found: C, 77.48; H, 7.85; N, 14.36.

4-allyl-1-phenyl-2-(pyridin-3-ylmethyl)piperazine (III-25). The reaction of 100 mg (0.462 mmol) of N^1, N^1 -diallyl- N^2 -phenylethane-1,2-diamine (III-22) with 111 mg (0.554 mmol) of 3-bromo-pyridine was conducted for 10 h according to the general procedure using $\text{P}(\text{2-furyl})_3$ as the ligand (4 mol %). Upon purification, 87 mg (56 %) of the title compound was obtained as an orange solid, m.p. 59–61 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.31 (t, $J = 7.5$ Hz, 2 H), 7.04 (d, $J = 8.5$ Hz, 2 H), 6.98 (d, $J = 8$ Hz, 2 H), 6.84 (t, $J = 7.5$ Hz, 1 H), 6.69 (d, $J = 8.5$ Hz, 2 H), 5.98–5.89 (m, 1 H), 5.22–5.15 (m, 2 H), 3.87–3.84 (m, 1 H), 3.35 (dt, $J = 2.5, 12$ Hz, 1 H), 3.25–3.16 (m, 1 H), 3.11–3.01 (m, 2 H), 3.01–2.90 (m, 8 H), 2.86–2.83 (m, 1 H), 2.49 (dd, $J = 2.5, 13$ Hz, 1 H), 2.27 (td, $J = 3.5, 11$ Hz, 1 H), 2.10 (dd, $J = 3, 11$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.9, 149.2, 135.4, 130.1, 129.4, 128.3, 118.8, 118.0, 115.8, 113.1, 61.9, 58.4, 53.8, 53.6, 43.6, 41.0, 31.5; IR (film) 2952, 2798, 1615 cm^{-1} . Anal calcd for $\text{C}_{22}\text{H}_{29}\text{N}_3$: C, 78.76; H, 8.71; N, 12.53. Found: C, 78.59; H, 8.59; N, 12.27.

***tert*-Butyl-2-(allyl(benzyl)amino)-2-oxoethylcarbamate (III-27a)**. A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the *N*-*boc* glycine (**III-26**) (3.12 g, 17.81 mmol), DCC (7.34 g, 35.62 mmol) and 36 mL dichloromethane (0.5 M). The solution was stirred for 10 min at rt then *N*-benzyl-allyl amine (2.62g, 17.81 mmol) was added. The resulting mixture was stirred at room temperature for 12 h then filtered to remove the dicyclohexylurea byproduct. The resulting solution was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude *N*-*boc*-*N'*-allyl amino amide product was purified by flash chromatography on silica gel to provide a 4.72 g (87%) of the title compound as a white solid, which was contaminated with ca. 15% dicyclohexylurea and as a 1.5:1 mixture of rotamers. ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.27 (m, 3 H), 7.24–7.22 (m, 1 H), 7.13 (d, *J* = 7.6 Hz, 1 H) 5.79–5.65 (m, 1 H), 5.55 (s, 1 H), 5.30–5.09 (m, 2 H), 4.71–4.58 (m, 1.2 H), 4.50–4.45 (m, 0.8 H), 4.04–4.03 (m, 2 H), 3.84–3.82 (m, 0.4 H), 3.80–3.77 (m, 1.2 H), 3.69–3.67 (m, 0.4 H), 1.44 (s, 5.4 H), 1.39 (s, 3.6 H).

***tert*-Butyl-2-(allyl(benzyl)amino)ethylcarbamate (III-27b)**. A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the *tert*-butyl 2-(allyl(benzyl)amino)-2-oxoethylcarbamate (**III-27a**) (4.47 g, 14.68 mmol). Diethyl ether was added (22 mL) to provide a 0.67 M solution, which was cooled to 0 °C. A solution of lithium aluminum hydride in diethyl ether (30 mL, 1 M in diethyl ether, 30 mmol) was added dropwise and the reaction was stirred at 0 °C until the starting amide was consumed as judged by TLC analysis (ca. 2.5 h). Water (2 mL) was added dropwise, followed by 10 M aqueous NaOH (5 mL), and additional water (2 mL). The

resulting suspension was stirred at rt for 5–10 minutes, then decanted, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 2.04 g (48%) of the title compound as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.30–7.27 (m, 4 H), 7.25–7.19 (m, 1 H), 5.87–5.77 (m, 1 H) 5.17–5.10 (m, 2 H), 4.84 (s, 1 H), 3.54 (s, 2 H), 3.18–3.10 (m, 2 H), 3.05 (d, *J* = 6.4 Hz, 2 H), 2.51 (t, *J* = 6 Hz, 2 H), 1.40 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 156.2, 139.3, 135.6, 129.0, 128.4, 127.2, 118.0, 79.1, 58.2, 56.8, 52.6, 38.2, 28.6; IR (film) 3361, 2977, 1715 cm⁻¹. Anal calcd for C₁₇H₂₆N₂O₂: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.23; H, 9.09; N, 9.60.

***tert*-Butyl-4-benzyl-2-(4-cyanobenzyl)piperazine-1-carboxylate (III-28)**. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with 11.6 mg Pd(OAc)₂ (6 mol % Pd), 18.1 mg PPh₃ (8 mol %), sodium *tert*-butoxide (100 mg, 1.03 mmol, 1.2 equiv), and the 4-bromobenzonitrile (188 mg, 1.03 mmol, 1.2 equiv). The Schlenk tube was purged with nitrogen and 250 mg of *tert*-butyl 2-(allyl(benzyl)amino)ethylcarbamate (**III-27b**) was added as a solution in toluene (2.5 mL/0.5 mmol substrate). The Schlenk tube was then heated to 90 °C with stirring until the starting material has been consumed as judged by ¹H NMR analysis of an aliquot taken from the reaction mixture. The reaction mixture was then cooled to room temperature, saturated aqueous ammonium chloride (2–3 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel to afford 229 mg

(68%) of the title compound as a white solid, m.p. 129–133 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.53–7.50 (m, 0.4 H), 7.42 (d, *J* = 7.6 Hz, 1.6 H), 7.37–7.29 (m, 5 H), 7.14–7.00 (m, 2 H), 4.30–3.70 (m, 2 H), 3.60 (d, *J* = 12.8 Hz, 1 H), 3.28 (d, *J* = 12.4 Hz, 1 H), 3.18 (td, *J* = 2.8, 12.8 Hz, 1 H), 3.10–3.00 (m, 1 H), 2.96–2.80 (m, 2 H), 2.53 (d, *J* = 11.6 Hz, 1 H), 2.11 (td, *J* = 3.2, 12 Hz, 1 H), 1.96 (d, *J* = 9.6, 1 H), 1.37 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 154.4, 144.9, 138.0, 134.6, 132.0, 130.1, 129.3, 127.3, 119.0, 109.8, 79.8, 62.8, 53.5, 52.1, 40.3, 39.2, 36.2, 28.3; IR (film) 3400, 2916, 1691 cm⁻¹. MS (ESI) 392.2338 (392.2338 calcd for C₂₄H₂₉N₃O₂, M + H⁺).

Synthesis of Substrates (Scheme 25)

General Procedure 1: Conversion of *N*-Phenyl Amino Acids (III-42 and III-43) to *N*-Allyl-*N*-Benzyl-*N*'-Phenyl Amino Amides (III-44 and III-45). A flame-dried round-bottomed flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the *N*-phenyl amino acid substrate (1.0 equiv). THF was added to provide a 0.5 M solution, which was cooled to 0 °C and stirred. DEPBT¹⁸ (1.2 equiv) was added, followed immediately by *N*-benzylallylamine (1 equiv), and the resulting reaction mixture was stirred at 0 °C until the starting amine had been consumed as judged by crude ¹H NMR analysis of an aliquot (ca. 3–4 h). Aqueous sodium bicarbonate was then added at 0 °C, and the resulting yellow reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified via flash chromatography on silica gel.

(S)-N-Allyl-N-benzyl-3-phenyl-2-phenylaminopropionamide (III-44). General procedure 1 was employed for the coupling of (*S*)-3-phenyl-2-phenylaminopropionic acid¹⁶ (3.63 g, 15.0 mmol) with *N*-benzylallylamine (2.21 g, 15.0 mmol). This procedure afforded 3.79 g (68%) of the title compound as a yellow oil. The enantiopurity was judged to be 98% ee by chiral hplc analysis (chiralcel OJ-H, 10% isopropanol/hexanes, 1 mL/min, RT = 11.14 min and 18.44 min). This molecule was observed as a 1.5:1 mixture of rotamers; data are for the mixture. ¹H NMR (400 MHz, CDCl₃) δ 7.31–7.17 (m, 9 H), 7.14–7.09 (m, 2 H), 6.92–6.91 (m, 1 H), 6.77–6.71 (m, 1 H), 6.66 (d, *J* = 8.0 Hz, 1 H), 6.54 (d, *J* = 7.5 Hz, 1 H), 5.73–5.66 (m, 0.4 H), 5.47–5.39 (m, 0.6 H), 5.15–4.97 (m, 2 H), 4.74 (d, *J* = 14.5 Hz, 0.6 H), 4.56–4.53 (m, 1.4 H), 4.49 (s, 0.5 H), 4.32 (d, *J* = 14.5 Hz, 0.6 H), 4.22–4.17 (m, 0.7 H), 4.03 (d, *J* = 17 Hz, 0.5 H), 3.65 (dd, *J* = 6.5, 15 Hz, 0.5 H), 3.53 (d, *J* = 5.5 Hz, 1.2 H), 3.13–3.02 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 172.9, 172.8, 146.6, 146.5, 137.4, 137.3, 136.9, 136.2, 132.5, 132.4, 129.54, 129.50, 129.46, 129.43, 129.0, 128.7, 128.60, 128.56, 128.4, 127.7, 127.5, 126.9, 126.8, 126.5, 118.4, 118.1, 117.6, 114.3, 55.9, 55.6, 49.5, 48.7, 48.6, 46.4, 39.53, 39.49; IR (film) 3326, 3027, 1639 cm⁻¹. Anal. Calcd for C₂₅H₂₆N₂O: C, 81.05; H, 7.07; N, 7.56. Found: C, 80.90; H, 7.05; N, 7.50.

(S)-N-Allyl-N-benzyl-3-methyl-2-phenylaminobutyramide (III-45). General procedure 1 was employed for the coupling of (*S*)-3-methyl-2-phenylaminobutyric acid¹⁶ (1.27 g, 6.57 mmol) with *N*-benzylallylamine (967 mg, 6.57 mmol). This procedure afforded 1.37 g (65%) of the title compound as a tan solid, m.p. 48–55 °C. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OJ-H column, 10%

isopropanol/hexanes, 1 mL/min, RT = 7.40 min and 10.00 min). This molecule was observed as a 1.5:1 mixture of rotamers; data are for the mixture. ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.24 (m, 3 H), 7.16–7.14 (m, 2 H), 7.09–7.06 (m, 2 H), 6.73–6.66 (m, 2 H), 6.54 (d, 1 H), 5.76–5.66 (m, 1 H), 5.21–5.04 (m, 2 H), 4.88 (d, *J* = 14.5 Hz, 0.7 H), 4.70 (d, *J* = 17 Hz, 0.4 H), 4.46–4.28 (m, 2 H), 4.15 (s, 1 H), 3.97–3.93 (dd, *J* = 3.0, 17 Hz, 0.7 H), 3.84–3.79 (dd, *J* = 3.0, 17 Hz, 0.7 H), 3.60 (dd, *J* = 6.5, 15 Hz, 0.5 H), 2.09–2.08 (m, 1 H), 1.06–1.00 (m, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 173.6, 173.5, 148.25, 148.21, 137.2, 136.2, 132.7, 132.6, 129.2, 128.9, 128.6, 128.1, 127.7, 127.4, 126.6, 118.09, 118.07, 117.9, 117.7, 114.5, 114.4, 59.5, 59.2, 49.9, 48.8, 48.1, 48.0, 32.3, 32.2, 20.2, 20.1, 17.72, 17.68; IR (film) 3350, 2962, 1638 cm⁻¹. Anal. Calcd for C₂₁H₂₆N₂O: C, 78.22; H, 8.13; N, 8.69. Found: C, 77.96; H, 8.12; N, 8.68.

General Procedure 2: Reduction of *N*-Allyl-*N*-Benzyl-*N'*-Phenyl Amino Amides (III-44 and III-45) to *N*-Allyl-*N*-Benzyl-*N'*-Phenyl-1,2-Diamines (III-46 and III-47). A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the *N*-allyl-*N*-benzyl-*N'*-phenyl amino amide substrate (1.0 equiv). Diethyl ether was added to provide a 0.5 M solution, which was cooled to 0 °C with stirring. A solution of lithium aluminum hydride in diethyl ether (1 M, 2 equiv) was added dropwise, and the resulting mixture was stirred at 0 °C until the starting amide was completely consumed as judged by TLC analysis (ca. 2 h). Water (2 mL) was added dropwise, followed by 10 M aqueous NaOH (5 mL), and additional water (2 mL). The resulting suspension was stirred at rt for 5–10 minutes, then decanted, dried over

anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

(S)-N¹-Allyl-N¹-benzyl-3,N²-diphenyl-propane-1,2-diamine (III-46). General procedure 2 was conducted using (S)-N-allyl-N-benzyl-3-phenyl-2-phenylaminopropionamide (III-44) (3.79 g, 10.22 mmol) as substrate. This procedure afforded 3.13 g (86%) of the title compound as a yellow oil that was judged to be 98% ee by chiral hplc analysis (chiralcel OD-H, 0.5% isopropanol/hexanes, 1 mL/min, RT = 11.15 min and 12.72 min), $[\alpha]_D^{23} -43.08^\circ$ (*c* 0.26, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.31–7.23 (m, 8 H), 7.21–7.14 (m, 5 H), 6.68 (t, *J* = 7.6 Hz, 1 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 5.89–5.79 (m, 1 H), 5.14–5.11 (m, 2 H), 3.93 (s, 1 H), 3.72–3.65 (m, 1 H), 3.62 (d, *J* = 13.6 Hz, 1 H), 3.51 (d, *J* = 13.6 Hz, 1 H), 3.14–3.01 (m, 2 H), 2.92 (dd, *J* = 5.2, 14.0 Hz, 1 H), 2.80 (dd, *J* = 7.2, 14.4 Hz, 1 H), 2.57–2.47 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 148.1, 139.3, 138.7, 135.5, 129.6, 129.4, 129.2, 128.4, 127.2, 126.3, 118.0, 117.3, 113.4, 58.7, 57.4, 56.9, 52.3, 39.2 (one aromatic carbon signal is absent due to accidental equivalence); IR (film) 3400, 2957, 1600 cm⁻¹. Anal. Calcd for C₂₅H₂₈N₂: C, 84.23; H, 7.92; N, 7.86. Found: C, 84.23; H, 7.98; N, 7.87.

(S)-N¹-Allyl-N¹-benzyl-3-methyl-N²-phenyl-butane-1,2-diamine (III-47) General procedure 2 was conducted using (S)-N-allyl-N-benzyl-3-methyl-2-phenylaminobutyramide (III-45) (1.34 g, 4.16 mmol) as substrate. This procedure afforded 1.13 g (88%) of the title compound as a yellow oil that was judged to be 99% ee by chiral hplc analysis (chiralcel OD-H, 0.1% isopropanol/hexanes, 0.2 mL/min, RT = 31.65 min and 35.18 min), $[\alpha]_D^{23} -59.5^\circ$ (*c* 0.98, CH₂Cl₂). ¹H NMR (500 MHz, CDCl₃)

δ 7.31–7.23 (m, 5 H), 7.22–7.12 (m, 2 H), 6.65 (t, $J = 7.5$, 1 H), 6.56 (d, $J = 8.5$ Hz, 2 H), 5.88 (ddt, $J = 6.0, 10.5, 16.5$ Hz, 1 H), 5.18–5.13 (m, 2 H), 3.72 (s, 1 H), 3.63 (d, $J = 13.5$ Hz, 1 H), 3.50 (d, $J = 13.5$ Hz, 1 H), 3.37–3.33 (m, 1 H), 3.11 (dd, $J = 6.0, 14.5$ Hz, 1 H), 3.04 (dd, $J = 7.0, 13.5$ Hz, 1 H), 2.52–2.44 (m, 2 H), 2.13–2.06 (m, 1 H), 0.87 (dd, $J = 4.5, 7.0$ Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.1, 139.7, 136.0, 129.4, 129.2, 128.4, 127.1, 117.8, 116.8, 113.2, 58.9, 57.5, 55.9, 54.3, 29.5, 18.6, 17.5; IR (film) 3400, 3025, 1601 cm^{-1} . Anal. Calcd for $\text{C}_{21}\text{H}_{28}\text{N}_2$: C, 81.77; H, 9.15; N, 9.08. Found: C, 81.73; H, 9.21; N, 9.09.

General Procedure 3: Conversion of *N*-Boc Amino Acids to *N*-Boc-*N'*-Allyl-1,2-Diamines (III-53-III-57). A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the *N*-boc amino acid (1.0 equiv), DCC (2.0 equiv) and a sufficient volume of dichloromethane to provide a solution with a 0.5 M amine concentration. The solution was stirred for 30 min at rt then the appropriate allylamine derivative (1.0 equiv) was added. The resulting mixture was stirred at room temperature for 12 h then filtered to remove the dicyclohexylurea byproduct. The resulting solution was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude *N*-boc-*N'*-allyl amino amide product was purified by flash chromatography on silica gel. In some cases the purified product was contaminated with small amounts of dicyclohexyl urea. This material was carried on without further purification.

A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the *N*-boc-*N'*-allyl amino amide (1.0 equiv). Diethyl ether was

added to provide a 0.5 M solution, which was cooled to 0 °C. A solution of lithium aluminum hydride in diethyl ether (1 M, 2.0 equiv) was added dropwise and the reaction was stirred at 0 °C until the starting amide was consumed as judged by TLC analysis (ca. 3 h). Water (2 mL) was added dropwise, followed by 10 M aqueous NaOH (5 mL), and additional water (2 mL). The resulting suspension was stirred at rt for 5–10 minutes, then decanted, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.

(*R*)-*tert*-Butyl-1-[allyl(benzyl)amino]-3-(benzyloxy)propan-2-ylcarbamate (III-53).

General procedure 3 was used for the coupling of (*S*)-3-(benzyloxy)-2-(*tert*-butoxycarbonylamino)propanoic acid (5.99 g, 20.28 mmol) with *N*-benzylallylamine (2.98 g, 20.28 mmol). This procedure afforded 7.67 g (89%) of (*S*)-*tert*-butyl 1-[allyl(benzyl)amino]-3-(benzyloxy)-1-oxopropan-2-ylcarbamate (**III-48**) as a white solid, which was contaminated with ca. 15% dicyclohexylurea. This material was carried on without further purification. The enantiopurity was judged to be 98% ee by chiral hplc analysis (chiralcel OD column, 5% isopropanol/hexanes, 1 mL/min, RT = 7.19 min and 9.13 min). This molecule was isolated as a 4.6:1 mixture of rotamers; data are for the mixture. ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.28 (m, 6 H), 7.20–7.17 (m, 4 H), 5.82–5.69 (m, 1 H), 5.43 (m, 0.8 H), 5.26–5.07 (m, 2 H), 4.99–4.97 (m, 0.2 H), 4.71–4.53 (m, 3.8 H), 4.44–4.40 (m, 0.2 H), 4.17–4.07 (m, 0.2 H), 4.02–3.96 (m, 1.8 H), 3.86–3.79 (m, 2.8 H), 3.71–3.66 (m, 0.2 H), 1.43 (m, 9 H).

The (*S*)-*tert*-butyl 1-[allyl(benzyl)amino]-3-(benzyloxy)-1-oxopropan-2-ylcarbamate (**III-48**) product of the DCC coupling reaction (7.65 g, 18.0 mmol) was reduced

following general procedure 3. This procedure afforded 4.83 g (65%) of the title compound as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.31–7.17 (m, 10 H), 5.80 (dt, $J = 6.8, 10.4$ Hz, 1 H), 5.15–5.08 (m, 2 H), 4.81 (s, 1 H), 4.42–4.35 (m, 2 H), 3.80 (s, 1 H), 3.65–3.58 (m, 2 H), 3.51–3.44 (m, 2 H), 3.11 (dd, $J = 8.0, 14.4$ Hz, 1 H), 3.01 (dd, $J = 6.4, 14.4$ Hz, 1 H), 2.64 (dd, $J = 7.6, 12.8$ Hz, 1 H), 2.47 (dd, $J = 6.0, 12.4$ Hz, 1 H), 1.41 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.9, 139.7, 138.5, 136.0, 129.1, 128.5, 128.4, 127.80, 127.77, 127.1, 117.7, 79.3, 73.4, 70.2, 58.6, 57.3, 54.5, 48.9, 28.6; IR (film) 3436, 2976, 1713 cm^{-1} ; MS (ESI) 411.2637 (411.2648 calcd for $\text{C}_{25}\text{H}_{34}\text{N}_2\text{O}_3$, $\text{M} + \text{H}^+$).

(*S*)-*tert*-Butyl-1-(diallylamino)propan-2-ylcarbamate (III-54). General procedure 3 was used for the coupling of (*S*)-2-*tert*-butoxycarbonylaminopropionic acid (1.16 g, 6.13 mmol), with diallylamine (595 mg, 754 μL , 6.13 mmol). This procedure afforded 1.64 g (100%) of (*S*)-*tert*-butyl 1-(diallylamino)-1-oxopropan-2-ylcarbamate (**III-49**) as a white solid, which was contaminated with 5% dicyclohexylurea. This material was carried on without further purification. This molecule was observed as a 5:1 mixture of rotamers. Data are for the mixture ^1H NMR (500 MHz, CDCl_3) δ 5.83–5.70 (m, 2 H), 5.39 (d, $J = 7.5$ Hz, 0.8 H), 5.25–5.11 (m, 4 H), 4.99–4.96 (m, 0.2 H), 4.59–4.57 (m, 0.8 H), 4.43–4.41 (m, 0.2 H), 4.18–4.10 (m, 0.2 H), 4.06–3.88 (m, 3.6 H), 3.70–3.60 (m, 0.2 H), 1.43 (s, 9 H), 1.31 (d, $J = 6.5$ Hz, 3 H).

The (*S*)-*tert*-butyl-1-(diallylamino)-1-oxopropan-2-ylcarbamate product (**III-49**) of the DCC coupling reaction (1.64 g, 6.16 mmol) was reduced with lithium aluminium hydride following general procedure 3. This procedure afforded 1.13 g (72%) of the title

compound as a white solid, m.p. 45–47 °C. ¹H NMR (500 MHz, CDCl₃) δ 5.85–5.77 (m, 2 H), 5.18–5.11 (m, 4 H), 4.68 (s, 1 H), 3.67–3.63 (m, 1 H), 3.12 (dd, *J* = 6.0, 14 Hz, 2 H), 3.04 (dd, *J* = 6.5, 14 Hz, 2 H), 2.40–2.30 (m, 2 H), 1.44 (s, 9 H), 1.12 (d, *J* = 6.5 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 156.0, 135.9, 117.7, 79.1, 58.7, 57.3, 44.8, 28.7, 19.7; IR (film) 3326, 2930, 1690 cm⁻¹; MS (EI) 254.2003 (254.1994 calcd for C₁₄H₂₆N₂O₂, M + H⁺).

***tert*-Butyl-1-(allyl(benzyl)amino)propan-2-ylcarbamate (III-55).** General procedure 3 was used for the coupling of 2-(*tert*-butoxycarbonylamino)propanoic acid (4.5 g, 23.78 mmol) and *N*-Benzylallylamine (3.50 g, 23.78 mmol). This procedure afforded 7.57 g (100 %) of *tert*-butyl 1-(allyl(benzyl)amino)-1-oxopropan-2-ylcarbamate (**III-50**) as a white solid, which was contaminated with ca. 15% of dicyclohexylurea as a white solid, contaminated with DCU as a 1.25:1 mixture of rotamers ¹H NMR (300 MHz, CDCl₃) δ 7.38–7.28 (m, 3 H), 7.20–7.18 (m, 2 H), 5.83–5.68 (m, 1 H), 5.43 (s, 1 H), 5.26–5.06 (m, 2 H), 4.70–4.52 (m, 3 H), 4.03–3.91 (m, 1 H), 3.87–3.80 (m, 1 H), 1.44 (s, 5 H), 1.42 (s, 4 H), 1.34 (m, *J* = 6.9 Hz, 1.8 H), 1.27 (d, *J* = 6.9 Hz, 1.2 H); ¹³C NMR (100 MHz, CDCl₃) δ 173.8, 155.3, 137.2, 136.4, 132.7, 132.5, 129.1, 128.8, 128.1, 128.0, 127.6, 127.0, 117.9, 79.8, 50.2, 49.2, 48.4, 48.0, 46.5, 28.6, 19.8; IR (film) 3306, 2978, 1703, 1648 cm⁻¹. MS (ESI) 341.1834 (341.1841 calcd for C₁₈H₂₆N₂O₃, M + Na⁺).

The (*S*)-*tert*-butyl 1-(allyl(benzyl)amino)-1-oxopropan-2-ylcarbamate (**III-50**) coupling product of the DCC reaction (1.52 g, 4.77 mmol) was reduced with lithium aluminum hydride following general procedure 3. This procedure afforded 900 mg (62%) of the title compound as a white solid, m.p. 37–39 °C. ¹H NMR (500 MHz, CDCl₃) δ

7.31–7.29 (m, 3 H), 7.25–7.22 (m, 2 H), 5.89–5.81 (m, 1 H), 5.19–5.13 (m, 2 H), 4.58 (s, 1 H), 3.78–3.68 (m, 1 H), 3.64 (d, $J = 14$ Hz, 1 H), 3.51 (d, $J = 14$ Hz, 1 H), 3.14–3.10 (m, 1 H), 3.06–3.02 (m, 1 H), 2.41–2.31 (m, 2 H), 1.46 (s, 9 H), 1.10 (d, $J = 6$ Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 156.0, 139.6, 135.8, 129.1, 128.4, 127.2, 117.9, 79.2, 59.0, 58.5, 57.2, 44.7, 28.7, 19.7; IR (film) 3350, 2360, 1702 cm^{-1} . Anal. Calcd for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_2$: C, 71.02; H, 9.27; N, 9.20. Found: C, 71.12; H, 9.55; N, 9.42.

(*S*)-tert-Butyl-1-[allyl(4-methoxyphenyl)amino]propan-2-ylcarbamate (III-56).

General procedure 3 was used for the coupling of (*S*)-2-tert-butoxycarbonylamino propionic acid (828 mg, 4.38 mmol) and *N*-*p*-methoxyphenylallylamine^{16,49} (710 mg, 4.38 mmol). This procedure afforded 1.28 g (88%) of (*S*)-tert-butyl 1-[allyl(4-methoxyphenyl)amino]-1-oxopropan-2-ylcarbamate (**III-51**) as a white solid, which was contaminated with ca. 15% of dicyclohexylurea. ^1H NMR (500 MHz, CDCl_3) δ 7.13 (d, $J = 8.5$ Hz, 2 H), 6.92 (d, $J = 9.5$ Hz, 2 H), 5.82 (ddt, $J = 6.0, 11.0, 17$ Hz, 1 H), 5.28 (d, $J = 8.0$ Hz, 1 H), 5.12 (dd, $J = 1.5, 11$ Hz, 1 H), 5.07 (dd, $J = 1.5, 17$ Hz, 1 H), 4.34–4.27 (m, 2 H), 4.18–4.11 (m, 1 H), 3.82 (s, 3 H), 1.41 (s, 9 H), 1.11 (d, $J = 6.5$ Hz, 3 H).

The (*S*)-tert-butyl 1-[allyl(4-methoxyphenyl)amino]-1-oxopropan-2-ylcarbamate (**III-51**) coupling product of the DCC reaction (1.28 g, 3.83 mmol) was reduced with lithium aluminum hydride following general procedure 3. This procedure afforded 4.83 g (65%) of the title compound as a white solid, m.p. 99–102 °C. ^1H NMR (400 MHz, CDCl_3) δ 6.84–6.75 (m, 4 H), 5.85–5.76 (m, 1 H), 5.14–5.10 (m, 2 H), 4.46 (s, br, 1 H), 3.95–3.76 (m, 3 H), 3.74 (s, 3 H), 3.36 (dd, $J = 6.0, 14.4$ Hz, 1 H), 3.05 (dd, $J = 5.6, 14.4$ Hz, 1 H),

1.43 (s, 9 H), 1.16 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.6, 152.0, 143.5, 134.5, 116.7, 115.2, 114.9, 57.3, 55.9, 55.3, 45.7, 29.9, 28.6, 19.2; IR (film) 3357, 1676 cm^{-1} ; MS (EI) 320.2095 (320.2100 calcd for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_3$).

***tert*-Butyl-1-(allyl(benzyl)amino)-4-methylpentan-2-ylcarbamate (III-57).** General procedure 3 was used for the coupling of 2-(*tert*-butoxycarbonylamino)-4-methylpentanoic acid (1.70 g, 7.35 mmol) with *N*-benzylallylamine (1.08 g, 7.35 mmol) with the only difference being the use of DCC as a 3 M solution (the amount of CH_2Cl_2 was adjusted appropriately to provide a 0.5 M solution). This procedure afforded 2.65 g (100%) of (*S*)-*tert*-butyl 1-[allyl(benzyl)amino]-3-(benzyloxy)-1-oxopropan-2-ylcarbamate (III-52) as a white solid, which was contaminated with ca. 15% dicyclohexylurea. This material was carried on without further purification. This molecule was isolated as a 1.2:1 mixture of rotamers; data are for the mixture. ^1H NMR (400 MHz, CDCl_3) δ 7.36–7.28 (m, 2.72 H), 7.22–7.19 (m, 2.27 H), 5.84–5.70 (m, 1 H), 5.26–5.09 (m, 3 H), 4.70–4.62 (m, 2 H), 4.60–4.51 (m, 1 H), 4.07–3.98 (m, 1 H), 3.87–3.80 (m, 1 H), 1.78–1.71 (m, 2 H), 1.44 (s, 4.9 H), 1.42 (s, 4.1 H), 1.36–1.27 (m, 1 H), 0.97–0.88 (m, 6 H), 0.84 (d, $J = 6.8$ Hz, 0.55 H), 0.77 (d, $J = 6.4$ Hz, 0.45 H).

The *tert*-butyl 1-(allyl(benzyl)amino)-4-methyl-1-oxopentan-2-ylcarbamate (III-52) product of the DCC coupling reaction (2.62 g, 7.26 mmol) was reduced following general procedure 3. This procedure afforded 1.57 g (62%) of the title compound as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.34–7.28 (m, 4 H), 7.24–7.21 (m, 1 H), 5.90–5.80 (m, 1 H), 5.19–5.12 (m, 2 H), 4.29 (s, 1 H), 3.80–3.70 (m, 1 H), 3.65 (dd, $J = 13.6$ Hz, 1 H), 3.53 (dd, $J = 13.6$ Hz, 1 H), 3.16–3.02 (m, 2 H), 2.37 (d, $J = 6.8$ Hz, 2 H),

1.72–1.62 (m, 1 H), 1.46 (s, 9 H), 1.34–1.29 (m, 1H), 1.22–1.15 (m, 1 H), 0.90 (d, $J = 6.8$ Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.0, 139.8, 136.1, 129.1, 128.3, 127.0, 117.6, 79.0, 58.7, 58.5, 57.4, 47.3, 43.4, 28.7, 25.0, 23.5, 22.5; IR (film) 3359, 2956, 1703 cm^{-1} . MS (ESI) 347.2702 (347.2699 calcd for $\text{C}_{21}\text{H}_{34}\text{N}_2\text{O}_2, \text{M} + \text{H}^+$).

General Procedure 4: Conversion of *N*-Boc-*N'*-Allyl-1,2-diamines (III-53-III-57) to *N*-aryl-*N'*-Allyl-1,2-diamines (III-58-III-62). A flask equipped with magnetic stirbar was charged with the appropriate *N*-Boc-*N'*-allyl-1,2-diamine (1.0 equiv) and a sufficient volume of dioxane to provide a 0.1 M solution. A solution of 4 M aqueous HCl (33 equiv) was added and the reaction mixture was heated to 50 °C for 2 h. The reaction mixture was cooled to room temperature and NH_4OH was added dropwise until the solution pH was >11. The resulting mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to afford the corresponding primary amine product. The crude product was immediately carried on without further purification.

A flame dried Schlenk tube equipped with a magnetic stirbar was charged with $\text{Pd}_2(\text{dba})_3$ (1 mol % complex, 2 mol % Pd), (\pm)-BINAP (2 mol %), sodium *tert*-butoxide (1.2 equiv), the appropriate aryl bromide (1.0 equiv), and a 0.5 M solution of the primary amine (1.0 equiv) in toluene. The reaction mixture was heated to 80 °C with stirring until the starting material had been consumed as judged by TLC analysis (ca. 6 h). The mixture was cooled to rt and a solution of aqueous ammonium chloride was added (4 mL). The resulting mixture was extracted with ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

(R)-4-{1-[Allyl(benzyl)amino]-3-(benzyloxy)propan-2-ylamino}benzonitrile (III-63).

General procedure 4 was used for the deprotection of (*R*)-*tert*-butyl 1-[allyl(benzyl)amino]-3-(benzyloxy)propan-2-ylcarbamate (**III-53**) (3.9 g, 9.51 mmol). This procedure afforded 3.1 g (100%) of (*S*)-*N*¹-allyl-*N*¹-benzyl-3-benzyloxypropane-1,2-diamine (**III-58**) as a yellow oil. The crude product was immediately subjected to the subsequent reaction without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.21 (m, 10 H), 5.86 (dt, *J* = 6, 11 Hz, 1 H), 5.17–5.12 (m, 2 H), 4.50 (s, 2 H), 3.67 (d, *J* = 13.5 Hz, 1 H), 3.51–3.48 (m, 2 H), 3.30–3.26 (m, 1 H), 3.20–3.12 (m, 2 H), 3.00 (dd, *J* = 5.4, 7.5 Hz, 1 H), 2.46–2.38 (m, 2 H), 1.60 (s, 2 H); MS (ESI) 311.2116 (311.2123 calcd for C₂₀H₂₆N₂O, M + H⁺).

General procedure 4 was used for the *N*-arylation of (*S*)-*N*¹-allyl-*N*¹-benzyl-3-benzyloxypropane-1,2-diamine (**III-58**) (900 mg, 2.89 mmol) with 4-bromobenzonitrile (527 mg, 2.89 mmol). This procedure afforded 864 mg (73%) of the title compound as an orange oil. The enantiopurity was judged to be 98% ee by chiral hplc analysis (chiralcel AD column, 0.7% isopropanol/hexanes, 1 mL/min, RT = 24.75 min and 28.10 min), [α]_D²³ –25.59° (*c* 0.79, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.28 (m, 12 H), 6.40 (d, *J* = 8.5 Hz, 2 H), 5.85 (dt, *J* = 6.5, 10.5 Hz, 1 H), 5.22–5.16 (m, 2 H), 4.54 (d, *J* = 6.5 Hz, 1 H), 4.49–4.44 (m, 2 H), 3.67 (dd, *J* = 3.0, 9.0 Hz, 1 H), 3.65–3.56 (m, 2 H), 3.53–3.46 (m, 2 H), 3.17–3.10 (m, 2 H), 2.74 (dd, *J* = 7.5, 13.5 Hz, 1 H), 2.60 (dd, *J* = 6.5, 13.5 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 151.0, 139.5, 138.0, 135.6, 133.8, 129.1, 128.6, 128.5, 127.99, 127.90, 127.4, 120.7, 118.1, 112.7, 98.6, 73.5, 69.9, 59.3, 58.3, 54.3, 51.4; IR (film) 3365, 2211, 1606 cm⁻¹; MS (ESI) 412.2383 (412.2389 calcd for C₂₇H₂₉N₃O, M + H⁺).

(S)-N¹,N¹-Diallyl-N²-phenylpropane-1,2-diamine (III-64). General procedure 4 was used for the deprotection of 1.08 g (4.24 mmol) of (*S*)-*tert*-butyl 1-(diallylamino)propan-2-ylcarbamate (**III-54**) (1.08 g, 4.24 mmol). This procedure afforded 654 mg (85%) of (*S*)-N¹,N¹-diallylpropane-1,2-diamine (**III-59**) as a yellow oil. The crude product was immediately subjected to the subsequent reaction without further purification. ¹H NMR (500 MHz, CDCl₃) δ 5.95–5.87 (m, 2 H), 5.19–5.15 (m, 4 H), 3.70 (s, br, 2 H), 3.36–3.30 (m, 1 H), 3.24–3.20 (m, 2 H), 3.13–3.10 (m, 2 H), 2.66 (dd, *J* = 10.5, 15 Hz, 1 H), 2.53 (dd, *J* = 4.5, 14 Hz, 1 H), 1.40 (d, *J* = 6.5 Hz, 3 H).

General procedure 4 was used for the *N*-arylation of (*S*)-N¹,N¹-diallylpropane-1,2-diamine (**III-59**) (379 mg, 2.46 mmol) with bromobenzene (386 mg, 2.46 mmol). This procedure afforded 390 mg (69%) of the title compound as a yellow oil. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OJ-H column, 1% IPA/hexanes, 0.2 mL/min, RT = 38.71 min and 43.68 min), [α]_D²³ –4.61° (*c* 0.23, CH₂Cl₂). ¹H NMR (500 MHz, CDCl₃) δ 7.18–7.15 (m, 2 H), 6.69 (t, *J* = 7.5 Hz, 1 H), 6.64 (d, *J* = 8.5 Hz, 2 H), 5.83 (ddt, *J* = 6.5, 7.0, 10 Hz, 2 H), 5.18–5.12 (m, 4 H), 4.20 (s, 1 H), 3.50–3.43 (m, 1 H), 3.17 (dd, *J* = 6.0, 14 Hz, 2 H), 3.04 (dd, *J* = 7.0, 14.5 Hz, 2 H), 2.54 (dd, *J* = 8.5, 13 Hz, 1 H), 2.42 (dd, *J* = 6.0, 13 Hz, 1 H), 1.19 (d, *J* = 6.0 Hz, 3 H); ¹³C (100 MHz, CDCl₃) δ 148.4, 135.7, 129.3, 117.7, 117.3, 113.7, 59.0, 57.2, 46.6, 19.9; IR (film) 3350, 2924, 1602 cm⁻¹; MS (EI) 230.1787 (230.1783 calcd for C₁₅H₂₂N₂).

N¹-allyl-N¹-benzyl-N²-phenylpropane-1,2-diamine (III-65). General procedure 4 was used for the deprotection of *tert*-butyl 1-(allyl(benzyl)amino)propan-2-ylcarbamate (**III-55**) (890 mg, 2.93 mmol). This procedure afforded 526 mg (88%) of N¹-allyl-N¹-

benzylpropane-1,2-diamine (**III-60**) as a yellow oil. The crude product was immediately subjected to the subsequent reaction without further purification. ^1H NMR (500 MHz, CDCl_3) δ 7.33–7.29 (m, 3 H), 7.25–7.22 (m, 2 H), 5.91–5.83 (m, 1 H), 5.18–5.13 (m, 2 H), 3.75–3.70 (m, 1 H), 3.43 (d, $J = 13.5$ Hz, 1 H), 3.21–3.17 (m, 1 H), 3.04–2.99 (m, 1 H), 2.98–2.94 (m, 1 H), 2.33–2.30 (m, 1 H), 2.26–2.22 (m, 1 H), 1.47 (s, 2 H), 0.99 (d, $J = 6$ Hz, 3 H).

General procedure 4 was used for the *N*-arylation of *N*¹-allyl-*N*¹-benzylpropane-1,2-diamine (**III-60**) (278 mg, 1.36 mmol) with 214 mg bromobenzene (144 μl , 1.36 mmol). This procedure afforded 270 mg (71%) of the title compound as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.37–7.31 (m, 4 H), 7.30–7.27 (m, 1 H), 7.23–7.20 (m, 2 H), 6.73 (tt, $J = 1, 7.5$ Hz, 1 H), 6.64 (dd, $J = 1, 8.5$ Hz, 2 H), 5.96–5.88 (m, 1 H), 5.25–5.19 (m, 2 H), 4.14 (s, 1 H), 3.73 (d, $J = 13$ Hz, 1 H), 3.57–3.50 (m, 2 H), 3.23–3.19 (m, 1 H), 3.12–3.08 (m, 1 H), 2.64–2.60 (m, 1 H), 2.50–2.46 (m, 1 H), 1.22 (d, $J = 6.5$ Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 148.4, 139.5, 135.7, 129.4, 129.2, 128.5, 127.2, 118.0, 117.3, 113.6, 59.4, 58.7, 57.3, 46.7, 19.9; IR (film) 3360, 2806, 1602 cm^{-1} . MS (ESI) 281.2015 (281.2018 calcd for $\text{C}_{19}\text{H}_{24}\text{N}_2$, $\text{M} + \text{H}^+$).

(*S*)-*N*¹-Allyl-*N*²-(4-chlorophenyl)-*N*¹-(4-methoxyphenyl)propane-1,2-diamine (III-66**)**. General procedure 4 was used for the deprotection of (*S*)-*tert*-butyl 1-[allyl(4-methoxyphenyl)amino]propan-2-ylcarbamate (**III-56**) (513 mg, 1.60 mmol). This procedure afforded 318 mg (91%) of (*S*)-*N*¹-allyl-*N*¹-(4-methoxyphenyl)propane-1,2-diamine (**III-61**) as a yellow oil. The crude product was immediately subjected to the

subsequent reaction without further purification. ^1H NMR (500 MHz, CDCl_3) δ 6.81 (d, $J = 9.0$ Hz, 2 H), 6.75 (d, $J = 9.0$ Hz, 2 H), 5.86–5.79 (m, 1 H), 5.14–5.11 (m, 2 H), 3.90 (dd, $J = 1.5, 5.0$ Hz, 2 H), 3.75 (s, 3 H), 3.26–3.21 (m, 1 H), 3.20 (d, $J = 4.5$ Hz, 1 H), 3.00–2.96 (m, 1 H), 1.60 (s, br, 2 H), 1.09 (d, $J = 6.0$ Hz, 3 H).

General procedure 4 was used for the *N*-arylation of (*S*)-*N*¹-allyl-*N*¹-(4-methoxyphenyl)propane-1,2-diamine (**III-61**) (64 mg, 0.29 mmol) with 4-chlorobromobenzene (55 mg, 0.29 mmol). This procedure afforded 65 mg (69%) of the title compound as a yellow oil. The enantiopurity was judged to be 98% ee by chiral hplc analysis (chiralcel OD column, 1% isopropanol/hexanes, 0.2 mL/min, RT = 59.14 min and 63.37 min), $[\alpha]_{\text{D}}^{23} +21.46^\circ$ (*c* 0.11, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 7.08 (d, $J = 8.8$ Hz, 2 H), 6.83 (d, $J = 9.2$ Hz, 2 H), 6.75 (d, $J = 9.2$ Hz, 2 H), 6.48 (d, $J = 8.8$ Hz, 2 H), 5.86–5.77 (m, 1 H), 5.16–5.11 (m, 2 H), 3.95–3.79 (m, 2 H), 3.77 (s, 3 H), 3.74–3.63 (m, 2 H), 3.32–3.22 (m, 2 H), 1.22 (d, $J = 6.4$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.5, 146.4, 143.6, 134.6, 129.2, 121.9, 116.9, 116.2, 114.9, 114.6, 57.8, 55.9, 55.7, 48.0, 19.5; IR (film) 3391, 2929, 1598 cm^{-1} ; MS (EI) 330.1490 (330.1500 calcd for $\text{C}_{19}\text{H}_{23}\text{ClN}_2$).

***N*¹-allyl-*N*¹-benzyl-4-methyl-*N*²-phenylpentane-1,2-diamine (**III-67**).** General procedure 4 was used for the deprotection of *tert*-butyl 1-(allyl(benzyl)amino)-4-methylpentan-2-ylcarbamate (**III-57**) (1.49 g, 4.30 mmol). This procedure afforded 1.06 g (100%) of *N*¹-allyl-*N*¹-benzyl-4-methylpentane-1,2-diamine (**III-62**) as a yellow oil. The crude product was immediately subjected to the subsequent reaction without further

purification. ¹H NMR (500 MHz, CDCl₃) δ 7.31–7.28 (m, 4 H), 7.25–7.22 (m, 1 H), 5.91–5.83 (m, 1 H), 5.18–5.13 (m, 2 H), 3.77 (d, *J* = 13.5 Hz, 1 H), 3.40 (d, *J* = 13.5 Hz, 1 H), 3.23–3.19 (m, 1 H), 2.96–2.91 (m, 2 H), 2.34–2.31 (m, 1 H), 2.27–2.23 (m, 1 H), 1.75–1.68 (m, 1 H), 1.53 (s, 2 H), 1.15–1.06 (m, 2 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 0.86 (d, *J* = 7 Hz, 3 H).

General procedure 4 was used for the *N*-arylation of *N*¹-allyl-*N*¹-benzyl-4-methylpentane-1,2-diamine (**III-62**) (1.06 g, 4.30 mmol) with bromobenzene (453 μL, 4.30 mmol). This procedure afforded 1.09 g (79%) of the title compound as a yellow oil. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OJ-H column, 5% isopropanol/hexanes, 1 mL/min, RT = 6.16 min and 8.90 min). ¹H NMR (500 MHz, CDCl₃) δ 7.32–7.27 (m, 4 H), 7.25–7.22 (m, 1 H), 7.13 (td, *J* = 7.5 Hz, 2 H), 6.65 (t, *J* = 7.0 Hz, 1 H), 6.54 (d, *J* = 8 Hz, 2 H), 5.90–5.82 (m, 1 H), 5.18–5.13 (m, 2 H), 3.72 (d, *J* = 6 Hz, 1 H), 3.63 (d, *J* = 13.5 Hz, 1 H), 3.56 (d, *J* = 13.5 Hz, 1 H), 3.48–3.41 (m, 1 H), 3.14–3.06 (m, 2 H), 2.55–2.45 (m, 2 H), 1.77–1.69 (m, 1 H), 1.50–1.45 (m, 1 H), 1.38–1.32 (m, 1 H), 0.96 (d, *J* = 7 Hz, 3 H), 0.88 (d, *J* = 6.5 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 148.6, 139.8, 135.9, 129.4, 129.2, 128.4, 127.2, 117.8, 117.0, 113.2, 59.2, 58.3, 57.8, 49.8, 43.6, 25.1, 23.3, 23.1; IR (film) 3400, 2954, 1601 cm⁻¹. MS (ESI) 323.2471 (323.2487 calcd for: C₂₂H₃₀N₂, M + H⁺).

Synthesis of Piperazines via Coupling with Aryl Bromides (Table 10)

General Procedure for Pd-Catalyzed Synthesis of *N*-Aryl Disubstituted Piperazines.

A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream

of nitrogen and charged with Pd₂(dba)₃ (1 mol % complex, 2 mol % Pd), P(2-furyl)₃ (8 mol %), sodium *tert*-butoxide (1.2 equiv), and the aryl bromide (1.2 equiv). The Schlenk tube was purged with nitrogen and the amine was added as a solution in toluene (2.5 mL/0.5 mmol substrate). The Schlenk tube was then heated to 105 °C with stirring until the starting material has been consumed as judged by ¹H NMR analysis of an aliquot taken from the reaction mixture. The reaction mixture was then cooled to room temperature, saturated aqueous ammonium chloride (2–3 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

(2*S*,6*R*)-2,4-Dibenzyl-6-(4-*tert*-butylbenzyl)-1-phenylpiperazine (III-71). The reaction of 150 mg (0.42 mmol) of *N*¹-allyl-*N*¹-benzyl-3,*N*²-diphenylpropane-1,2-diamine (**III-46**) with 108 mg (0.51 mmol) of 4-bromo-*tert*-butylbenzene was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ¹H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 132 mg (64%) of the title compound was obtained as a white solid, m.p. 74–77 °C. This material was judged to be of >20:1 dr by ¹H NMR analysis. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OJ-H column, 2 % isopropanol/hexanes, 0.1 mL/min, RT = 55.13 min and 101.14 min), [α]_D²³ + 5.48° (*c* 0.27, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.38 (m, 7 H), 7.24–7.17 (m, 5 H), 7.07–6.99 (m, 6 H), 6.83 (t, *J* = 7.2 Hz, 1 H), 3.80 (d, *J* = 6.4 Hz, 2 H), 3.54–3.44 (m, 2 H), 3.07 (t, *J* = 12.8 Hz, 2 H), 2.94–2.87 (m, 2 H), 2.79 (t, *J* = 11.2 Hz, 2 H), 2.15–2.07

(m, 2 H), 1.31 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.0, 147.1, 140.4, 139.0, 137.3, 130.1, 129.9, 129.5, 129.1, 128.7, 128.6, 127.5, 126.2, 125.6, 117.4, 113.5, 63.2, 55.6, 55.5, 54.5, 54.1, 37.5, 36.9, 34.6, 31.6; IR (film) 2960, 1597 cm^{-1} ; MS (ESI) 489.3272 (489.3270 calcd for $\text{C}_{35}\text{H}_{40}\text{N}_2$, $\text{M} + \text{H}^+$).

(2*S*,6*R*)-2,4-Dibenzyl-6-(4-methoxybenzyl)-1-phenylpiperazine (III-68). The reaction of 150 mg (0.42 mmol) of N^1 -allyl- N^1 -benzyl-3, N^2 -diphenylpropane-1,2-diamine (III-46) with 95 mg (0.51 mmol) of 4-bromoanisole was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ^1H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 120 mg (62%) of the title compound was obtained as a white solid, m.p. 119–122 °C. This material was judged to be of >20:1 dr by ^1H NMR analysis. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OJ-H column, 10 % isopropanol/hexanes, 0.5 mL/min, RT = 15.12 min and 30.50 min), $[\alpha]_D^{23} +13.51^\circ$ (c 0.48, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 7.47–7.38 (m, 7 H), 7.26–7.18 (m, 3 H), 7.06 (d, J = 8.0 Hz, 4 H), 6.95 (d, J = 8.4 Hz, 3 H), 6.84 (t, J = 6.0 Hz, 1 H), 6.77 (d, J = 8.4 Hz, 1 H), 3.83–3.74 (m, 5 H), 3.52–3.45 (m, 2 H), 3.11–2.99 (m, 2 H), 2.89 (d, J = 11.6 Hz, 2 H), 2.83–2.73 (m, 2 H), 2.13–2.10 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.1, 147.0, 140.3, 138.9, 132.4, 130.4, 130.1, 129.9, 129.5, 128.7, 128.6, 127.4, 126.2, 117.4, 114.1, 113.5, 63.2, 55.8, 55.6, 55.4, 54.3, 54.1, 37.5, 36.5; IR (film) 3026, 2812, 1597 cm^{-1} ; MS (ESI) 463.2744 (463.2749 calcd for $\text{C}_{32}\text{H}_{34}\text{N}_2\text{O}$, $\text{M} + \text{H}^+$).

(2*R*,6*S*)-tert-butyl 4-[(4,6-dibenzyl-1-phenylpiperazin-2-yl)methyl]benzoate (III-72).

The reaction of 150 mg (0.42 mmol) of N^1 -allyl- N^1 -benzyl-3, N^2 -diphenylpropane-1,2-

diamine (**III-46**) with 130 mg (0.51 mmol) of 4-bromo-*tert*-butylbenzoate was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ¹H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 132 mg (59%) of the title compound was obtained as a white solid, m.p. 75–77 °C. This material was judged to be of >20:1 dr by ¹H NMR analysis. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OD-H column, 5 % isopropanol/hexanes, 2 mL/min, RT = 1.40 min and 1.94 min), $[\alpha]_D^{23} + 35.1^\circ$ (*c* 0.30, CH₂Cl₂). ¹H NMR (500 MHz, CDCl₃) δ 7.85 (dd, *J* = 1.5, 6.5 Hz, 2 H), 7.47–7.40 (m, 7 H), 7.27–7.25 (m, 2 H), 7.24–7.18 (m, 1 H), 7.08–7.06 (m, 6 H), 6.87 (t, *J* = 7.0 Hz, 1 H), 3.82 (t, *J* = 11 Hz, 2 H), 3.49 (m, 2 H), 3.16–3.06 (m, 2 H), 2.91–2.81 (m, 4 H), 2.18–2.11 (m, 2 H), 1.61 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 165.9, 146.9, 145.2, 140.2, 138.7, 130.10, 130.06, 129.96, 129.86, 129.4, 129.3, 128.7, 128.6, 127.6, 126.3, 117.8, 113.7, 81.0, 63.1, 55.7, 55.5, 54.3, 54.1, 37.6, 37.4, 28.4; IR (film) 2975, 1711, 1598 cm⁻¹; MS (ESI) 533.3166 (533.3168 calcd for C₃₆H₄₀N₂O₂, M + H⁺).

(2*S*,6*R*)-4-Benzyl-2-(4-*tert*-butylbenzyl)-6-isopropyl-1-phenylpiperazine (III-73). The reaction of 150 mg (0.49 mmol) of *N*¹-allyl-*N*¹-benzyl-3-methyl-*N*²-phenylbutane-1,2-diamine (**III-47**) with 145 mg (0.68 mmol) of 4-bromo-*tert*-butylbenzene was conducted for 10 h according to the general procedure using 2 mol % Pd₂(dba)₃ and 16 mol % P(2-furyl)₃. The product was formed with >20:1 dr as judged by ¹H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 110 mg (51%) of the title compound was obtained as a white solid, m.p. 83–86 °C. This material was judged to be of >20:1 dr by ¹H NMR analysis. The enantiopurity was judged to be 99% ee by

chiral hplc analysis (chiralcel OD-H column, 100% hexanes, 1 mL/min, RT = 6.29 min and 7.06 min), $[\alpha]_D^{23} + 3.13^\circ$ (*c* 0.17, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.29 (m, 7 H), 7.24–7.18 (m, 4 H), 7.01 (t, *J* = 7.2 Hz, 1 H), 6.95 (d, *J* = 8.0 Hz, 2 H), 3.57 (d, *J* = 13.2 Hz, 1 H), 3.49–3.47 (m, 1 H), 3.44 (d, *J* = 16 Hz, 1 H), 3.30–3.27 (m, 1 H), 2.74–2.62 (m, 2 H), 2.57–2.54 (m, 1 H), 2.49–2.45 (m, 2 H), 2.37–2.32 (m, 1 H), 1.94–1.89 (m, 1 H), 1.32 (9 H), 0.90 (d, *J* = 6.8 Hz, 3 H), 0.81 (d, *J* = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 150.3, 148.8, 138.5, 136.8, 129.4, 129.3, 129.0, 128.3, 127.1, 125.2, 121.8, 63.4, 63.0, 60.7, 57.2, 53.7, 38.3, 34.5, 31.6, 29.8, 20.8, 18.2 (one aromatic carbon signal is absent due to accidental equivalence); IR (film) 2915, 1604 cm⁻¹. MS (ESI) 441.3269 (441.3270 calcd for C₃₁H₄₀N₂, M + H⁺).

(2*S*,6*R*)-4-Benzyl-2-isopropyl-6-(6-methoxynaphthalen-2-ylmethyl)-1-

phenylpiperazine (III-74). The reaction of 100 mg (0.32 mmol) of *N*¹-allyl-*N*¹-benzyl-3-methyl-*N*²-phenylbutane-1,2-diamine (III-47) with 108 mg (0.45 mmol) of 2-bromo-6-methoxynaphthalene was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ¹H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 77 mg (51%) of the title compound was obtained as a white solid, m.p. 114–119 °C. This material was judged to be of >20:1 dr by ¹H NMR analysis. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel AD column, 5% isopropanol/hexanes, 0.9 mL/min, RT = 4.22 min and 5.78 min), $[\alpha]_D^{23} + 33.5^\circ$ (*c* 0.34, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, *J* = 6.4, 8.8 Hz, 2 H), 7.36–7.26 (m, 7 H), 7.21–7.19 (m, 3 H), 7.13–7.07 (m, 3 H), 7.01 (t, *J* = 7.2 Hz, 1 H), 3.91 (s, 3 H), 3.56 (d, *J* = 12.8 Hz, 1 H), 3.54–3.49 (m, 1 H), 3.35 (d, *J* =

13.2 Hz, 1 H), 3.29–3.25 (m, 1 H), 2.86–2.73 (m, 2 H), 2.55 (dd, $J = 3.2, 10.8$ Hz, 1 H), 2.47–2.41 (m, 2 H), 2.35 (dd, $J = 6.4, 10.8$ Hz, 1 H), 1.93–1.87 (m, 1 H), 0.89 (d, $J = 6.8$ Hz, 3 H), 0.79 (d, $J = 7.2$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.4, 150.4, 138.5, 135.1, 133.2, 129.44, 129.36, 129.17, 129.16, 128.5, 128.4, 127.6, 127.2, 126.8, 122.0, 118.8, 105.8, 63.5, 63.2, 60.8, 57.3, 55.5, 53.7, 39.0, 29.8, 20.8, 18.2 (one aromatic carbon signal is absent due to accidental equivalence); IR (film) 2956, 1604 cm^{-1} ; MS (ESI) 465.2899 (465.2906 calcd for $\text{C}_{32}\text{H}_{36}\text{N}_2\text{O}$, $\text{M} + \text{H}^+$).

(2*R*,6*R*)-4-[4-Benzyl-2-benzyloxymethyl-6-(4-methylbenzyl)piperazin-1

yl]benzotrile (III-75). The reaction of 150 mg (0.37 mmol) of (*R*)-4-{1-[allyl(benzyl)amino]-3-(benzyloxy)propan-2-ylamino}benzotrile (III-63) with 75 mg (0.48 mmol) of 4-bromotoluene was conducted for 10 h according to the general procedure. The product was formed with 14:1 dr as judged by ^1H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 128 mg (70%) of the title compound was obtained as a white solid, m.p. 125–133 °C. This material was determined to contain a 14:1 mixture of diastereomers as judged by ^1H NMR analysis. The enantiopurity of the major diastereomer was judged to be 97% ee by chiral hplc analysis (chiralcel AD column, 10 % isopropanol/hexanes, 1 mL/min, RT = 5.32 min and 7.41 min), $[\alpha]_{\text{D}}^{23} +168.99^\circ$ (c 0.17, CH_2Cl_2). Data are for the major diastereomer: ^1H NMR (500 MHz, CDCl_3) δ 7.53 (d, $J = 9.0$ Hz, 2 H), 7.40–7.33 (m, 7 H), 7.32–7.28 (m, 3 H), 6.96 (d, $J = 8.0$ Hz, 2 H), 6.84 (d, $J = 9.0$ Hz, 2 H), 6.69 (d, $J = 8.0$ Hz, 2 H), 4.55–4.48 (m, 2 H), 3.95–3.89 (m, 2 H), 3.72–3.70 (m, 1 H), 3.61 (d, $J = 12$ Hz, 1 H), 3.39–3.35 (m, 2 H), 3.26 (dd, $J = 1.5, 11$ Hz, 1 H), 2.83 (d, $J = 11.5$ Hz, 1 H), 2.75 (t, $J = 12$

Hz, 1 H), 2.44 (d, $J = 12.5$ Hz, 1 H), 2.31–2.28 (m, 1 H), 2.28 (s, 3 H), 1.96 (dd, $J = 3.0$, 11 Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 150.2, 138.6, 138.2, 136.2, 135.8, 134.1, 129.8, 129.5, 129.2, 128.7, 128.6, 128.13, 128.06, 127.6, 120.6, 112.1, 99.6, 73.7, 68.5, 62.8, 55.0, 54.4, 53.1, 52.6, 37.0, 21.2; IR (film) 2919, 1603 cm^{-1} ; MS (ESI) 524.2679 (524.2678 calcd for $\text{C}_{34}\text{H}_{35}\text{N}_3\text{O}$, $\text{M} + \text{Na}^+$).

(2*R*,6*R*)-4-[4-Benzyl-2-benzyloxymethyl-6-(4-trifluoromethylbenzyl)piperazin-1-yl]benzotrile (III-76). The reaction of 150 mg (0.37 mmol) of (*R*)-4-{1-[allyl(benzyl)amino]-3-(benzyloxy)propan-2-ylamino}benzotrile (**III-63**) with 98 mg (0.44 mmol) of 4-bromobenzotrifluoride was conducted for 10 h according to the general procedure. The product was formed with 14:1 dr as judged by ^1H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 131 mg (65%) of the title compound was obtained as a white solid, m.p. 154–157 °C. This material was determined to contain a 14:1 mixture of diastereomers as judged by ^1H NMR analysis. The enantiopurity of the major diastereomer was judged to be 99% ee by chiral hplc analysis (chiralcel AD column, 10 % isopropanol/hexanes, 1 mL/min, RT = 5.99 min and 8.68 min), $[\alpha]_{\text{D}}^{23} + 155.58^\circ$ (c 0.13, CH_2Cl_2). The diastereomers were subsequently separated by careful flash chromatography on silica gel.

Major (*cis*) diastereomer (**III-76**): ^1H NMR (400 MHz, CDCl_3) δ 7.54 (d, $J = 8.0$ Hz, 2 H), 7.41–7.31(m, 12 H), 6.82 (t, $J = 8.8$ Hz, 4 H), 4.59–4.51 (m, 2 H), 3.97–3.89 (m, 2 H), 3.74–3.71 (m, 1 H), 3.66 (d, $J = 12.4$ Hz, 1 H), 3.38 (d, $J = 6.8$ Hz, 1 H), 3.32–3.27 (m, 2 H), 2.80 (t, $J = 12.4$ Hz, 1 H), 2.71 (d, $J = 11.6$, 1 H), 2.51 (d, $J = 12.4$ Hz, 1 H), 2.37 (dd, $J = 2.4$, 11.6 Hz, 1 H), 1.95 (dd, $J = 3.2$, 12 Hz, 1 H); ^{13}C NMR (500 MHz,

CDCl₃) δ 150.0, 142.8, 138.4, 138.1, 134.1, 130.0, 129.6, 129.0, 128.74, 128.69, 128.2, 128.1, 127.7, 125.6 (q, $J = 14.5$ Hz), 124.3 (q, $J = 270.5$ Hz), 120.4, 112.1, 99.1, 73.6, 68.4, 62.8, 54.7, 54.5, 53.2, 52.1, 37.3; IR (film) 2817, 1603 cm⁻¹; MS (ESI) 578.2402 (578.2395 calcd for C₃₄H₃₂F₃N₃O, M + Na⁺).

Minor (*trans*) diastereomer (**III-76b**): ¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, $J = 8.4$ Hz, 2 H), 7.37–7.26 (m, 11 H), 7.19–7.17 (m, 2 H), 7.10 (d, $J = 8.4$ Hz, 2 H), 6.79 (d, $J = 8.0$ Hz, 2 H), 4.38 (s, 2 H), 3.80–3.76 (m, 1 H), 3.68–3.62 (m, 2 H), 3.49 (dd, $J = 2.4, 9.6$ Hz, 1 H), 3.34–3.31 (m, 2 H), 3.19 (dd, $J = 2.4, 11.2$ Hz, 1 H), 3.03–2.97 (m, 1 H), 2.53–2.49 (m, 2 H), 2.46–2.41 (m, 1 H), 2.30 (dd, $J = 3.2, 11.2$ Hz, 1 H).

(2R,6S)-4-Allyl-2-(4-methoxybenzyl)-6-methyl-1-phenylpiperazine (III-77). The reaction of 124 mg (0.54 mmol) of (*S*)-*N*¹,*N*¹-diallyl-*N*²-phenylpropane-1,2-diamine (**III-64**) with 121 mg (0.65 mmol) of 4-bromoanisole was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ¹H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 91 mg (50%) of the title compound was obtained as a yellow oil. This material was judged to be of >20:1 dr by ¹H NMR analysis. The enantiopurity was judged to be 99% ee by chiral hplc analysis (OD-H column, 100% hexanes, 1 mL/min, RT = 19.75 min and 22.39 min), $[\alpha]_D^{23} + 112.18$ (*c* 0.26, CH₂Cl₂). ¹H NMR (500 MHz, CDCl₃) δ 7.35 (t, $J = 8.5$ Hz, 2 H), 7.17 (d, $J = 8.0$ Hz, 2 H), 7.07 (t, $J = 7.5$ Hz, 1 H), 6.98 (d, $J = 9.0$ Hz, 2 H), 6.79–6.76 (m, 2 H), 5.90–5.82 (m, 1 H), 5.20–5.12 (m, 2 H), 3.77 (s, 3 H), 3.45–3.40 (m, 1 H), 3.38–3.35 (m, 1 H), 3.06–3.01 (m, 1 H), 2.92–2.88 (m, 1 H), 2.71 (dd, $J = 2.0, 11$ Hz, 1 H), 2.57

(dd, $J = 3.5, 13.5$ Hz, 1 H), 2.51 (d, $J = 10$ Hz, 1 H), 2.44–2.40 (m, 1 H), 2.26–2.18 (m, 2 H), 0.94 (d, $J = 6.5$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.1, 149.2, 135.2, 131.8, 130.2, 129.4, 123.2, 118.1, 113.8, 61.9, 60.5, 60.4, 57.4, 55.4, 54.2, 37.9, 18.8 (one carbon signal is absent due to accidental equivalence); IR (film) 3400, 2929, 1597 cm^{-1} ; MS (ESI) 337.2263 (337.2280 calcd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}$, $\text{M} + \text{H}^+$).

(2R,6S)-4-benzyl-2-(4-*tert*-butylbenzyl)-6-methyl-1-phenylpiperazine (III-78). The reaction of 100 mg (0.357 mmol) of N^1 -allyl- N^1 -benzyl- N^2 -phenylpropane-1,2-diamine (**III-65**) with 92 mg (75 μl , 0.428 mmol) of 4-bromo-*tert*-butylbenzene was conducted for 10 h according to the general procedure. The product was formed with 9:1 dr as judged by ^1H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 81 mg (55%) of the title compound as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.43–7.31 (m, 6 H), 7.23 (d, $J = 8$ Hz, 2 H), 7.10 (d, $J = 7.6$ Hz, 2 H), 6.99–6.92 (m, 3 H), 3.66–3.63 (m, 3 H), 3.43 (d, $J = 12.8$, 1 H), 2.76–2.66 (m, 2 H), 2.60–2.58 (m, 2 H), 2.52–2.48 (m, 1 H), 2.38 (d, $J = 9.6$ Hz, 1 H), 1.32 (s, 9 H), 1.14 (d, $J = 6$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 148.8, 148.3, 138.6, 137.1, 129.53, 129.48, 129.0, 128.4, 127.3, 125.3, 120.4, 118.9, 63.2, 59.8, 58.2, 56.1, 51.5, 37.7, 34.5, 31.6, 18.5; IR (film) 2962, 2360, 1596 cm^{-1} . MS (ESI) 413.2957 (413.2957 calcd for $\text{C}_{29}\text{H}_{36}\text{N}_2$, $\text{M} + \text{H}^+$).

Minor (*trans*) diastereomer (**III-78b**): ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.30 (m, 7 H), 7.10–7.02 (m, 5 H), 6.70 (d, $J = 7.6$ Hz, 2 H), 3.68–3.60 (m, 1 H), 3.57–3.50 (m, 2 H), 3.40–3.34 (m, 1 H), 2.98 (t, $J = 11.6$ Hz, 1 H), 2.89 (d, $J = 11.2$ Hz, 1 H), 2.64 (d, $J =$

10.4 Hz, 1 H), 2.53 (d, $J = 11.2$ Hz, 1 H), 2.32 (d, $J = 9.6$ Hz, 1 H), 2.08 (t, $J = 10.4$ Hz, 1 H), 1.23 (s, 9 H), 0.99 (d, $J = 6$ Hz, 3 H).

(2*R*,6*S*)-2-Benzyl-1-(4-chlorophenyl)-4-(4-methoxyphenyl)-6-methylpiperazine (III-79).

The reaction of 47 mg (0.14 mmol) of N^1 -allyl- N^2 -(4-chlorophenyl)- N^1 -(4-methoxyphenyl)propane-1,2-diamine (III-66) with 22 mg (0.17 mmol) of bromobenzene was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ^1H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 29 mg (51%) of the title compound was obtained as a yellow oil. This material was judged to be of >20:1 dr by ^1H NMR analysis. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OD-H column, 1% isopropanol/hexanes, 0.5 mL/min, RT = 9.27 min and 10.30 min), $[\alpha]_D^{23} + 58.87^\circ$ (c 0.55, CH_2Cl_2). ^1H NMR (500 MHz, CDCl_3) δ 7.34–7.27 (m, 4 H), 7.21–7.18 (m, 1 H), 7.12–7.09 (m, 4 H), 6.86–6.81 (m, 4 H), 3.76 (s, 3 H), 3.59–3.55 (m, 1 H), 3.52–3.49 (m, 1 H), 3.25 (dd, $J = 3.5, 12$ Hz, 1 H), 3.07 (dd, $J = 3.0, 12$ Hz, 1 H), 2.92–2.88 (m, 2 H), 2.68 (dd, $J = 3.5, 13.5$ Hz, 1 H), 2.58 (dd, $J = 10.5, 13.5$ Hz, 1 H), 1.05 (d, $J = 6.5$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 154.2, 147.5, 146.0, 139.4, 129.5, 129.3, 128.7, 128.0, 126.5, 123.6, 118.9, 114.7, 60.2, 58.3, 55.8, 54.7, 53.8, 38.6, 18.5; IR (film) 2930, 1510 cm^{-1} ; MS (ESI) 407.1895 (407.1890 calcd for $\text{C}_{25}\text{H}_{27}\text{ClN}_2\text{O}$, $\text{M} + \text{H}^+$).

(2*R*,6*S*)-4-benzyl-2-(biphenyl-4-ylmethyl)-6-isobutyl-1-phenylpiperazine (III-80).

The reaction of 150 mg (0.465 mmol) of N^1 -allyl- N^1 -benzyl-4-methyl- N^2 -phenylpentane-1,2-diamine (III-67) with 130.1 mg (0.558 mmol) of 4-bromobiphenyl was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged

by ^1H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 126 mg (57%) of the title compound was obtained as a pale yellow viscous oil. This material was judged to be of >20:1 dr by ^1H NMR analysis. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OD-H column, 2 % isopropanol/hexanes, 1 mL/min, RT = 3.54 min and 4.23 min). ^1H NMR (400 MHz, CDCl_3) δ 7.56 (d, J = 7.6 Hz, 2 H), 7.45–7.38 (m, 6 H), 7.36–7.31 (m, 6 H), 7.06 (d, J = 8.4 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 2 H), 6.84 (t, J = 7.2 Hz, 1 H), 3.76–3.66 (m, 2 H), 3.57 (d, J = 13.2 Hz, 1 H), 3.48 (d, J = 12.8 Hz, 1 H), 2.95 (t, J = 12.8 Hz, 1 H), 2.82–2.73 (m, 3 H), 2.39 (dd, J = 3.6, 11.2 Hz, 1 H), 2.20 (dd, J = 3.2, 11.2 Hz, 1 H), 1.94–1.84 (m, 1 H), 1.53–1.44 (m, 1 H), 1.28–1.22 (m, 2 H), 0.95 (d, J = 6.4, 3 H), 0.89 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.7, 141.2, 139.5, 139.1, 138.9, 129.9, 129.6, 129.5, 128.9, 128.5, 127.4, 127.297, 127.260, 127.2, 118.3, 115.4, 63.1, 56.6, 56.2, 54.8, 52.8, 40.3, 37.6, 26.2, 24.4, 21.8; IR (film) 2954, 2360, 1595 cm^{-1} . MS (ESI) 475.3114 (475.3113 calcd for $\text{C}_{34}\text{H}_{38}\text{N}_2$, $\text{M} + \text{H}^+$).

Isolation and Characterization of Side Products III-69 and III-70

Side products **III-69** and **III-70** were isolated by careful chromatography of the crude mixture of products obtained from the $\text{Pd}_2(\text{dba})_3/\text{P}(o\text{-tol})_3$ -catalyzed reaction of **III-46** with 4-bromoanisole. These compounds were characterized by ^1H NMR and 2-D COSY analysis. Data are as follows:

(S)-4-allyl-6-(4-methoxybenzyl)-2-methyl-1-phenyl-1,2,3,4-tetrahydropyrazine (III-69). ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.31 (m, 4 H), 7.20–7.12 (m, 5 H), 6.99–6.97

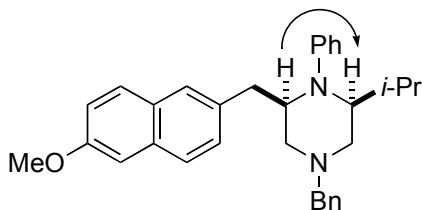
(m, 2 H), 6.89–6.85 (m, 1 H), 6.80–6.77 (m, 2 H), 6.75–6.73 (m, 2 H), 6.69 (d, $J = 8.0$ Hz, 1 H), 6.60 (dd, $J = 1.0, 8.5$ Hz, 2 H), 5.82 (s, 1 H), 4.08–3.98 (m, 2 H), 3.79 (s, 3 H), 3.56–3.52 (m, 1 H), 3.36 (d, $J = 10.5, 15.5$ Hz, 1 H), 3.14 (d, $J = 15$ Hz, 1 H), 2.74–2.66 (m, 2 H), 2.61–2.59 (m, 1 H), 2.49 (dd, $J = 5.0, 13$ Hz, 1 H).

(S)-4-allyl-2,6-dimethyl-1-phenyl-1,2,3,4-tetrahydropyrazine (III-70). ^1H NMR (500 MHz, CDCl_3) δ 7.34–7.19 (m, 10 H), 7.13–7.10 (m, 2 H), 6.82 (dt, $J = 1.0, 7.0$ Hz, 1 H), 6.56 (d, $J = 8.0$ Hz, 2 H), 5.68 (s, 1 H), 4.04–3.95 (m, 2 H), 3.67–3.64 (m, 1 H), 3.07 (dd, $J = 4.0, 13$ Hz, 1 H), 2.73–2.68 (m, 2 H), 2.62 (dd, $J = 2.5, 10.5$ Hz, 1 H), 1.73 (s, 3 H).

Assignment of Stereochemistry

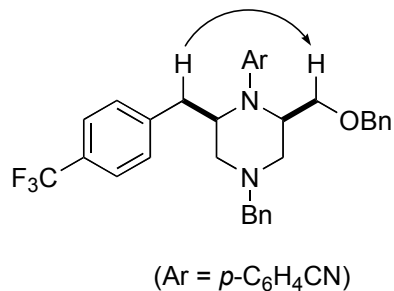
2-Isopropylpiperazines III-73 and III-74

The stereochemistry of 2-isopropylpiperazine **III-74** was assigned on the basis of 2D NOESY experiments. The key nOe signals are shown below. The stereochemistry of piperazine **III-73** was assigned based on analogy to **III-74**.



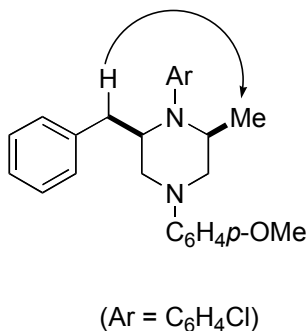
2-Benzyloxymethylpiperazines III-75 and III-76

The stereochemistry of 2-benzyloxymethylpiperazine **III-76** was assigned on the basis of 2D NOESY experiments. The key nOe signals are shown below. The stereochemistry of piperazine **III-75** was assigned based on analogy to **III-76**.



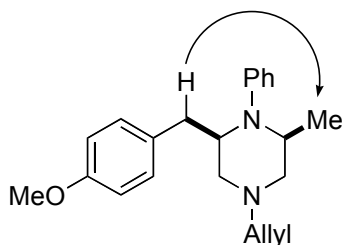
2-Methylpiperazine III-79

The stereochemistry of 2-methylpiperazine **III-79** was assigned on the basis of 2D NOESY experiments. The key nOe signals are shown below.



2-Methylpiperazine III-77 and 2-Benzylpiperazines III-71, III-68, and III-72

The stereochemistry of 2-methylpiperazine **III-77** was assigned on the basis of 2D NOESY experiments. The key nOe signals are shown below. The stereochemistry of 2-benzylpiperazines **III-71**, **III-68**, and **III-72** was assigned based on analogy to **III-77**.



Synthesis of Piperazines via Coupling with Vinyl Bromides (Table 11)

General Procedure for Pd-Catalyzed Synthesis of Piperazines. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with Pd₂(dba)₃ (2 mol % complex, 4 mol % Pd), P(2-furyl)₃ (16 mol %), sodium *tert*-butoxide (1.4 equiv), and the aryl bromide (1.4 equiv). The Schlenk tube was purged with nitrogen and the amine was added as a solution in toluene (2.5 mL/0.5 mmol substrate) or xylenes (2.5 mL/0.5 mmol substrate) as noted in each example. The Schlenk tube was then heated to 90 °C (toluene) or 135 °C (xylenes) with stirring until the starting material has been consumed as judged by ¹H NMR analysis of an aliquot taken from the reaction mixture. The reaction mixture was then cooled to room temperature, saturated aqueous ammonium chloride (2–3 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

(2*S*,6*R*)-2,4-dibenzyl-1-phenyl-6-((*E*)-3-(trimethylsilyl)allyl)piperazine (III-81). The reaction of 100 mg (0.281 mmol) of *N*¹-allyl-*N*¹-benzyl-*N*²,3-diphenylpropane-1,2-diamine (III-46) with 71 mg (61 μL, 0.393 mmol) of (*E*)-(2-bromovinyl)trimethylsilane in toluene (2.45 mL) at 90 °C was conducted for 10 h according to the general procedure to afford 76 mg (59%) of the title compound as a yellow viscous oil. This material was judged to be of >20:1 dr by ¹H NMR analysis. The enantiopurity was judged to be 97% ee by chiral hplc analysis (chiralcel OD-H column, 0.1% isopropanol/hexanes, 0.5 mL/min, RT = 8.68 min and 9.82 min). ¹H NMR (400 MHz, CDCl₃) δ 7.48–7.34 (m, 7

H), 7.27–7.18 (m, 3 H), 7.05 (d, $J = 6.8$ Hz, 2 H), 7.01 (d, $J = 8.4$ Hz, 2 H), 6.89 (t, $J = 7.2$ Hz, 1 H), 6.01–5.93 (m, 1 H), 5.62 (d, $J = 18.4$ Hz, 1 H), 3.82–3.79 (m, 1 H), 3.67–3.65 (m, 1 H), 3.58–3.50 (m, 2 H), 2.95 (t, $J = 12.4$ Hz, 1 H), 2.85–2.74 (m, 3 H), 2.69–2.61 (m, 1 H), 2.41–2.31 (m, 2 H), 2.22 (dd, $J = 3.2, 11.2$ Hz, 1 H), 0.06 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.4, 144.1, 140.3, 138.8, 133.6, 129.74, 129.68, 129.5, 128.6, 128.5, 127.4, 126.2, 118.3, 115.1, 63.2, 56.3, 55.3, 54.7, 53.7, 39.0, 37.6, -1.0; IR (film) 3026, 2953, 1597, 1500 cm^{-1} . MS (ESI) 455.2885 (455.2883 calcd for $\text{C}_{30}\text{H}_{38}\text{N}_2\text{Si}$, $\text{M} + \text{H}^+$).

(2*S*,6*R*)-2,4-dibenzyl-6-cinnamyl-1-phenylpiperazine (III-82). The reaction of 98 mg (0.274 mmol) of N^1 -allyl- N^1 -benzyl- N^2 ,3-diphenylpropane-1,2-diamine (**III-46**) with 71 mg (0.384 mmol) of (*E*)- β -bromostyrene in toluene (2.45 mL) at 90 °C was conducted for 10 h according to the general procedure to afford 92 mg (73%) of the title compound as a pale yellow solid, m.p. 43–48 °C. This material was judged to be of >20:1 dr by ^1H NMR analysis. The enantiopurity was judged to be 95% ee by chiral hplc analysis (chiralcel OJ-H column, 3% isopropanol/hexanes, 0.2 mL/min, RT = 65.89 min and 106.91 min). ^1H NMR (500 MHz, CDCl_3) δ 7.48–7.46 (m, 2 H), 7.44–7.36 (m, 5 H), 7.34–7.30 (m, 4 H), 7.25–7.17 (m, 4 H), 7.05–7.00 (m, 4 H), 6.87 (t, $J = 7$ Hz, 1 H), 6.29 (d, $J = 16$ Hz, 1 H), 6.21–6.15 (m, 1 H), 3.81 (d, $J = 9.5$ Hz, 1 H), 3.71 (d, $J = 9.0$ Hz, 1 H), 3.57–3.51 (m, 2 H), 3.00–2.93 (m, 2 H), 2.83–2.74 (m, 3 H), 2.42 (dd, $J = 6, 13.5$ Hz, 1 H), 2.33 (dd, $J = 3, 11$ Hz, 1 H), 2.20 (dd, $J = 3.0, 11.5$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.3, 140.3, 138.9, 137.7, 132.6, 129.8, 129.7, 129.5, 128.7, 128.6, 128.6, 128.0, 127.4, 127.3, 126.24, 126.21, 118.1, 114.6, 63.1, 56.1, 55.3, 54.4, 54.0,

37.6, 35.2; IR (film) 3025, 2923, 2811, 1596 cm^{-1} . MS (ESI) 459.2789 (459.2800 calcd for $\text{C}_{33}\text{H}_{34}\text{N}_2$, $\text{M} + \text{H}^+$).

(2*S*,6*R*)-4-benzyl-2-isopropyl-1-phenyl-6-(2-phenylallyl)piperazine (III-83). The reaction of 150 mg (0.487 mmol) of *N*¹-allyl-*N*¹-benzyl-3-methyl-*N*²-phenylbutane-1,2-diamine (III-47) with 125 mg (0.682 mmol) of α -bromostyrene in xylenes at 135 °C (2.45 mL) was conducted for 10 h according to the general procedure to afford 104 mg (52%) of the title compound as a yellow viscous oil. This material was judged to be of >20:1 dr by ¹H NMR analysis. The enantiopurity was judged to be 97% ee by chiral hplc analysis (chiralcel OD-H column, 0.1% isopropanol/hexanes, 0.5 mL/min, RT = 7.44 min and 8.68 min). ¹H NMR (400 MHz, CDCl_3) δ 7.32–7.27 (m, 6 H), 7.24–7.22 (m, 4 H), 7.10–7.03 (m, 5 H), 5.10 (s, 1 H), 4.92 (s, 1 H), 3.52–3.43 (m, 2 H), 3.12–3.03 (m, 2 H), 2.68–2.56 (m, 3 H), 2.39–2.32 (m, 1 H), 2.26–2.22 (m, 1 H), 2.10–2.05 (m, 1 H), 1.67–1.60 (m, 1 H), 0.82 (d, $J = 6.8$ Hz, 3 H), 0.73 (d, $J = 7.2$ Hz, 3 H); ¹³C NMR (100 MHz, CDCl_3) δ 150.1, 146.6, 141.0, 138.3, 129.3, 129.1, 128.3, 127.5, 127.1, 126.5, 124.6, 123.7, 114.8, 64.2, 63.4, 58.3, 57.9, 53.4, 39.1, 28.9, 20.5, 17.0; IR (film) 2958, 2360, 1596 cm^{-1} . MS (ESI) 411.2794 (411.2800 calcd for $\text{C}_{29}\text{H}_{34}\text{N}_2$, $\text{M} + \text{Na}^+$).

Synthesis of Piperazines via Coupling with Aryl Bromides (Table 12)

General Procedure for Pd-Catalyzed Synthesis of *N*-Boc Piperazines. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with $\text{Pd}(\text{OAc})_3$ (6 mol % Pd), $\text{P}(2\text{-furyl})_3$ (8 mol %), sodium *tert*-butoxide (1.2 (for III-85)—1.3 (for III-84) equiv), and the aryl bromide ((1.2 (for III-85)—1.3 (for III-

84) equiv). The Schlenk tube was purged with nitrogen and the amine was added as a solution in toluene (2.5 mL/0.5 mmol substrate). The Schlenk tube was then heated to 90 °C with stirring until the starting material has been consumed as judged by ¹H NMR analysis of an aliquot taken from the reaction mixture. The reaction mixture was then cooled to room temperature, saturated aqueous ammonium chloride (2–3 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

(2*R*,6*S*)-tert-butyl-4-benzyl-2-(4-cyanobenzyl)-6-methylpiperazine-1-carboxylate

(III-84). The reaction of 150 mg (0.493 mmol) of **(III-55)** with 117 mg (0.641 mmol) of 4-bromobenzonitrile in toluene (2.70 mL) at 90 °C was conducted for 10 h according to the general procedure to afford 135 mg (total yield of both diastereomers = 68%) of the title compound as a pale yellow solid, m.p. 180-185 °C. This material was judged to be of 1:1 dr by ¹H NMR analysis. Diastereomer 1 (*cis*): The enantiopurity both the *cis* and *trans* (below) diastereomer were judged to be 99% ee by chiral hplc analysis (chiralcel OJ-H column, 5% isopropanol/hexanes, 1.0 mL/min, RT = 7.40 min and 8.78 min). Diastereomer 1 (*cis*): ¹H NMR (500 MHz, CDCl₃) δ 7.38–7.35 (m, 7 H), 6.92 (d, *J* = 6.5 Hz, 2 H), 4.18–4.12 (m, 1 H), 3.89 (d, *J* = 10.5 Hz, 1 H), 3.63 (d, *J* = 13 Hz, 1 H), 3.24 (d, *J* = 13 Hz, 1 H), 3.07 (t, *J* = 11.5 Hz, 1 H), 2.77–2.73 (m, 2 H), 2.46 (d, *J* = 12 Hz, 1 H), 2.32 (dd, *J* = 4.5, 11.5 Hz, 1 H), 1.78 (dd, *J* = 4.0, 11.5 Hz, 1 H), 1.50 (s, 9 H), 1.37 (d, *J* = 7 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 154.9, 145.8, 138.8, 132.2, 130.4, 129.7,

128.6, 127.5, 119.3, 110.0, 80.0, 63.0, 58.9, 53.9, 52.3, 47.4, 40.6, 28.8, 21.1; IR (film) 2969, 2226, 1686 cm^{-1} . MS (ESI) 406.2496 (406.2495 calcd for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_2$, $\text{M} + \text{H}^+$).

Diastereomer 2 (*trans*) (**III-84b**): pale yellow solid, m.p. 109-114 °C. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OJ-H column, 5% isopropanol/hexanes, 0.2 mL/min, RT = 39.29 min and 42.49 min). ^1H NMR (500 MHz, CDCl_3) δ 7.40–7.31 (m, 7 H), 7.05 (d, $J = 8.0$ Hz, 2 H), 4.09–4.05 (m, 1 H), 3.72–3.65 (m, 1 H), 3.58 (d, $J = 13$ Hz, 1 H), 3.25 (d, $J = 12.5$ Hz, 1 H), 3.19–3.14 (m, 1 H), 2.86–2.78 (m, 2 H), 2.44–2.41 (m, 1 H), 2.04–2.00 (m, 2 H), 1.48 (s, 9 H), 1.39 (d, $J = 6$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.4, 145.3, 138.3, 132.2, 130.3, 129.6, 128.5, 127.5, 119.3, 110.0, 80.2, 62.9, 61.6, 55.9, 52.7, 48.5, 37.4, 28.7, 20.7; IR (film) 2972, 2226, 1704 cm^{-1} . MS (ESI) 406.2498 (406.2495 calcd for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_2$, $\text{M} + \text{H}^+$).

(Rac)-tert-butyl 4-benzyl-2-(4-cyanobenzyl)-6-isobutylpiperazine-1-carboxylate (III-85). The reaction of 54 mg (0.156 mmol) of (**III-57**) with 35 mg (0.187 mmol) of 4-bromobenzonitrile in toluene (0.80 mL) at 90 °C was conducted for 10 h according to the general procedure to afford 50 mg (total yield of both diastereomers = 72%) the title compound as a pale yellow oil. This material was judged to be of 2:1 dr by ^1H NMR analysis. Major (*cis*) diastereomer: ^1H NMR (300 MHz, CDCl_3) δ 7.40–7.30 (m, 7 H), 7.08–6.92 (m, 2 H), 4.02–3.88 (m, 2 H), 3.56 (d, $J = 12.9$ Hz, 1 H), 3.30 (d, $J = 12.6$ Hz, 1 H), 3.06 (t, $J = 11.7$ Hz, 1 H), 2.78 (t, $J = 14.1$ Hz, 2 H), 2.49–2.41 (m, 1 H), 2.17 (dd, $J = 3.9, 11.1$ Hz, 1 H), 2.04–1.92 (m, 1 H), 1.83 (dd, $J = 4.2, 11.4$ Hz, 1 H), 1.50–1.40 (m, 9 H), 1.17–1.09 (m, 1 H), 0.97–0.92 (m, 6 H).

Minor (*trans*) diastereomer (**III-85b**): ^1H NMR (400 MHz, CDCl_3) δ 7.48 (d, $J = 8.4$ Hz, 2 H), 7.39–7.27 (m, 5 H), 7.22 (d, $J = 8$ Hz, 2 H), 3.95–3.91 (m, 1 H), 3.85–3.80 (m, 1 H), 3.64 (d, $J = 12.8$ Hz, 1 H), 3.37 (d, $J = 13.2$ Hz, 1 H), 3.28 (dd, $J = 5.2, 12.8$ Hz, 1 H), 3.03–2.97 (m, 1 H), 2.67 (dd, $J = 3.6, 11.6$ Hz, 1 H), 2.45–2.40 (m, 2 H), 2.37–2.33 (m, 1 H), 1.78–1.72 (m, 1 H), 1.47 (s, 10 H), 1.25–1.10 (m, 1 H), 0.87 (t, $J = 6$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.2, 145.5, 138.6, 132.2, 130.3, 129.1, 128.5, 127.4, 119.3, 110.1, 80.1, 63.0, 55.6, 55.2, 53.9, 52.6, 41.6, 38.5, 28.7, 25.4, 23.3, 22.5.

***N*¹-allyl-*N*¹-benzyl-*N*²-(4-methoxyphenyl)propane-1,2-diamine (III-100)**. General procedure 4 was used for the *N*-arylation of *N*¹-allyl-*N*¹-benzylpropane-1,2-diamine (185 mg, 0.905 mmol) with 170 mg 4-bromoanisole (114 μL , 0.905 mmol) using 2 mol of di-*tert*-butylphosphino(*o*-biphenyl) in place of BINAP as the ligand. This procedure afforded 228 mg (81%) of the title compound as an orange oil. ^1H NMR (500 MHz, CDCl_3) δ 7.36–7.32 (m, 4 H), 7.30–7.26 (m, 1 H), 6.82–6.79 (m, 2 H), 6.64–6.60 (m, 2 H), 5.94–5.86 (m, 1 H), 5.23–5.18 (m, 2 H), 3.97 (s, 1 H), 3.78 (s, 3 H), 3.72 (d, $J = 13.5$ Hz, 1 H), 3.54 (d, $J = 13$ Hz, 1 H), 3.45–3.39 (m, 1 H), 3.22–3.18 (m, 1 H), 3.09–3.05 (m, 1 H), 2.62–2.58 (m, 1 H), 2.47–2.44 (m, 1 H), 1.19 (d, $J = 6$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 152.2, 142.6, 139.4, 135.7, 129.1, 128.4, 127.2, 117.9, 115.2, 115.0, 59.6, 58.7, 57.3, 55.9, 47.6, 20.0; IR (film) 3350, 2928, 2360, 1510 cm^{-1} . MS (ESI) 311.2126 (311.2123 calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}$, $\text{M} + \text{H}^+$).

4-(1-(allyl(benzyl)amino)propan-2-ylamino)benzotrile (III-101). General procedure 4 was used for the *N*-arylation of *N*¹-allyl-*N*¹-benzylpropane-1,2-diamine (278 mg, 1.36

mmol) with 248 mg 4-bromobenzonitrile (1.36 mmol). This procedure afforded 290 mg (70%) of the title compound as an orange oil. ^1H NMR (500 MHz, CDCl_3) δ 7.39–7.37 (m, 1 H), 7.32–7.24 (m, 5 H), 6.46 (d, $J = 7.5$ Hz, 2 H), 5.90–5.82 (m, 1 H), 5.21–5.17 (m, 2 H), 4.49 (d, $J = 4.5$ Hz, 1 H), 3.68 (d, $J = 13.5$ Hz, 1 H), 3.50–3.44 (m, 2 H), 3.21–3.17 (m, 1 H), 3.08–3.04 (m, 1 H), 2.57–2.52 (m, 1 H), 2.50–2.46 (m, 1 H), 1.14 (d, $J = 6$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.4, 139.3, 135.4, 133.8, 129.1, 128.5, 127.4, 120.8, 118.2, 112.7, 98.3, 59.1, 59.0, 57.8, 46.5; IR (film) 3361, 2807, 2211, 1607 cm^{-1} . MS (ESI) 306.1962 (306.1970 calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3$, $\text{M} + \text{H}^+$).

***N*¹-benzyl-*N*¹-(4-methoxyphenyl)-*N*²-phenylpropane-1,2-diamine (III-105)** General procedure 4 was used for the *N*-arylation of *N*¹-benzyl-*N*¹-(4-methoxyphenyl)propane-1,2-diamine (350 mg, 1.59 mmol) with 250 mg bromobenzene (168 μl , 1.36 mmol). This procedure afforded 308 mg (65%) of the title compound as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.19 (t, $J = 7.5$ Hz, 2 H), 6.88–6.85 (m, 2 H), 6.82–6.78 (m, 2 H), 6.72 (t, $J = 7$ Hz, 1 H), 6.62 (d, $J = 8$ Hz, 2 H), 5.90–5.82 (m, 1 H), 5.20–5.16 (m, 2 H), 3.98–3.93 (m, 1 H), 3.89–3.85 (m, 1 H), 3.80–3.72 (m, 5 H), 3.39–3.35 (m, 1 H), 3.29–3.25 (m, 1 H), 1.27 (d, $J = 6.5$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 152.3, 147.8, 143.7, 134.6, 129.4, 117.5, 116.8, 115.9, 114.8, 113.5, 57.8, 55.9, 55.6, 47.8, 19.7; IR (film) 2929, 2341, 1601 cm^{-1} . MS (ESI) 297.1964 (297.1967 calcd for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}$, $\text{M} + \text{H}^+$).

4-benzyl-2-(4-*tert*-butylbenzyl)-1-(4-methoxyphenyl)-6-methylpiperazine (III-102).

The reaction of 65 mg (0.209 mmol) of *N*¹-allyl-*N*¹-benzyl-*N*²-(4-methoxyphenyl)propane-1,2-diamine (III-100) with 54 mg (44 μl , 0.251 mmol) of 4-

bromo-*tert*-butylbenzene was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ¹H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 45 mg (49%) of the title compound as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.31 (d, *J* = 4 Hz, 4 H), 7.25–7.24 (m, 1 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 7.17 (d, *J* = 8.5 Hz, 2 H), 6.92–6.89 (m, 4 H), 3.82 (s, 3 H), 3.64 (d, *J* = 13 Hz, 1 H), 3.35–3.29 (m, 2 H), 3.16–3.06 (m, 1 H), 2.76 (t, *J* = 11 Hz, 2 H), 2.58 (dd, *J* = 3.5, 13.5 Hz, 1 H), 2.31–2.26 (m, 1 H), 2.16 (t, *J* = 10 Hz, 1 H), 2.02 (t, *J* = 9.5 Hz, 1 H), 1.29 (s, 9 H), 0.78 (d, *J* = 6 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 156.9, 148.8, 142.6, 138.2, 136.5, 129.4, 129.1, 128.9, 128.3, 127.2, 125.2, 114.4, 63.2, 62.2, 60.5, 58.9, 56.3, 55.6, 38.6, 34.5, 31.6, 19.0; IR (film) 2961, 2360, 1508 cm⁻¹. MS (ESI) 443.3060 (443.3062 calcd for C₃₀H₃₈N₂O, M + H⁺).

4-allyl-2-(4-*tert*-butylbenzyl)-6-methyl-1-phenylpiperazine (III-106). The reaction of 50 mg (0.217 mmol) of *N*¹, *N*¹-diallyl-*N*²-phenylpropane-1,2-diamine (**III-64**) with 56 mg (46 μl, 0.260 mmol) of 4-bromo-*tert*-butylbenzene was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ¹H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 35 mg (46%) of the title compound as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.32 (m, 2 H), 7.27–7.24 (m, 2 H), 7.16 (d, *J* = 7.6 Hz, 2 H), 7.04 (t, *J* = 7.2 Hz, 1 H), 7.00 (d, *J* = 8.4 Hz, 2 H), 5.93–5.82 (m, 1 H), 5.21–5.13 (m, 2 H), 3.51–3.46 (m, 1 H), 3.44–3.36 (m, 1 H), 3.08–3.03 (m, 1 H), 2.93–2.88 (m, 1 H), 2.69 (d, *J* = 8.8 Hz, 1 H), 2.62–2.58 (m, 1 H), 2.53–2.46 (m, 2 H), 2.34–2.30 (m, 1 H), 2.25–2.21 (m, 1 H), 1.29 (s, 9 H), 0.96 (d, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 149.0, 148.9, 136.7, 135.3, 129.4, 129.0, 125.3,

122.8, 118.1, 114.6, 61.9, 60.2, 60.0, 57.4, 53.9, 38.1, 34.5, 31.6, 18.8; IR (film) 2962, 1596 cm^{-1} . MS (ESI) 363.2798 (363.2800 calcd for $\text{C}_{25}\text{H}_{34}\text{N}_2$, $\text{M} + \text{H}^+$).

4-(4-benzyl-2-(4-*tert*-butylbenzyl)-6-methylpiperazin-1-yl)benzotrile (III-103). The reaction of 142 mg (0.466 mmol) of 4-(1-(allyl(benzyl)amino)propan-2-ylamino)benzotrile (**III-101**) with 120 mg (98 μl , 0.559 mmol) of 4-bromo-*tert*-butylbenzene was conducted for 10 h according to the general procedure. The product was formed with 6:1 dr as judged by ^1H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 156 mg (76%) of the title compound was isolated as a yellow solid (6:1 pure dr) major diastereomer m.p. 59–66 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) 7.56 (d, $J = 8.8$ Hz, 2 H), 7.47–7.38 (m, 5 H), 7.21 (d, $J = 6.8$ Hz, 2 H), 6.88–6.84 (m, 4 H), 4.04–3.99 (m, 1 H), 3.84–3.78 (m, 1 H), 3.62 (d, $J = 12.4$ Hz, 1 H), 3.46 (d, $J = 12.4$ Hz, 1 H), 3.09 (t, $J = 12.4$ Hz, 1 H), 2.94–2.86 (m, 2 H), 2.61 (d, $J = 12.8$ Hz, 1 H), 2.40 (dd, $J = 4.4, 10.8$ Hz, 1 H), 1.99 (dd, $J = 3.2, 11.6$ Hz, 1 H), 1.40 (d, $J = 6.8$ Hz, 3 H), 1.31 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.2, 149.3, 138.6, 136.4, 134.0, 129.6, 129.0, 128.6, 127.5, 125.6, 120.7, 112.3, 98.0, 63.0, 58.8, 55.2, 53.2, 48.2, 37.3, 34.5, 31.5, 18.3; IR (film) 2962, 2360, 1603 cm^{-1} . MS (ESI) 438.2905 (438.2909 calcd for $\text{C}_{30}\text{H}_{35}\text{N}_3$, $\text{M} + \text{H}^+$).

Minor (*trans*) diastereomer (**III-103b**) (isolated as 2:1 mixture with major diastereomer **III-103**): ^1H NMR (400 MHz, CDCl_3) δ 7.59–7.52 (m, 2 H), 7.44–7.30 (m, 5 H), 7.18 (d, $J = 8.4$ Hz, 1 H), 7.11–7.08 (m, 2 H), 6.86–6.82 (m, 2 H), 6.70 (d, $J = 8$ Hz, 1 H), 3.70–3.66 (m, 2 H), 3.62–3.54 (m, 1 H), 3.42 (t, $J = 14$ Hz, 1 H), 3.11–2.99 (m, 1 H),

2.95–2.84 (m, 2 H), 2.44–2.36 (m, 2 H), 2.09–2.03 (m, 1 H), 1.24 (s, 9 H), 1.02 (d, $J = 5.6$ Hz, 3 H).

***tert*-butyl 4-benzyl-2-(4-*tert*-butylbenzyl)-6-methylpiperazine-1-carboxylate (III-104).** The reaction of 50 mg (0.164 mmol) of *N*¹-allyl-*N*¹-(4-methoxyphenyl)-*N*²-phenylpropane-1,2-diamine (III-55) with 42.7 mg (35 μ L, 0.197 mmol) of 4-bromo-*tert*-butylbenzene was conducted for 10 h according to the general procedure (for *N*-aryl piperazines). The product was formed with 1:1 dr as judged by ¹H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 7 mg (9.8%) of the title compound as a yellow oil. One diastereomer was isolated as a ~3:1 mixture of diastereomers, while the other diastereomer was only isolated as a mixture of diastereomers with other material (either the other diastereomer or with a side product originating from β -hydride elimination prior to reductive elimination). Data are for the more purely isolated diastereomer. The reaction was repeated using conditions more suitable for the Boc-protected diamines. Therefore, 100 mg (0.329 mmol) of the amine Pd(OAc)₂ (4.73 mg, 6 mol%) and PPh₃ (6.6 mg, 8 mol %) and 1.3 eq of the 4-Br-*t*-Bu-benzene (75 μ L, 0.428 mmol) and NaOtBu (42 mg, 0.429 mmol) to afford 50 mg (35%) of the title compound. ¹H NMR (500 MHz, CDCl₃) δ 7.40–7.28 (m, 6 H), 7.20–7.14 (m, 2 H), 6.91 (d, $J = 8.0$ Hz, 1 H), 4.18–4.10 (m, 1 H), 3.98–3.93 (m, 1 H), 3.51 (d, $J = 12.8$ Hz, 1 H), 3.39 (d, $J = 13.2$ Hz, 1 H), 3.06 (t, $J = 12$ Hz, 1 H), 2.73–2.63 (m, 3 H), 2.21 (dd, $J = 4.4, 10.8$ Hz, 1 H), 1.83 (dd, $J = 4.0, 11.6$ Hz, 1 H), 1.51 (s, 9 H), 1.37 (d, $J = 6.8$ Hz, 3 H), 1.27 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 155.0, 148.8, 139.0, 137.1, 129.4, 129.3, 129.2, 128.5, 127.3, 125.4, 125.3, 79.7, 63.1, 58.4, 63.1, 58.4, 54.3, 53.2, 40.2,

34.5, 31.6, 28.8, 28.7, 21.0 (^{13}C contains 4 extra peaks from minor diastereomer); IR (film) 2965, 1690 cm^{-1} . MS (ESI) 437.3162 (437.3168 calcd for $\text{C}_{28}\text{H}_{40}\text{N}_2\text{O}_2$, $\text{M} + \text{H}^+$).

2-(4-*tert*-butylbenzyl)-4-(4-methoxyphenyl)-6-methyl-1-phenylpiperazine (III-107).

The reaction of 68 mg (0.229 mmol) of *N*¹-allyl-*N*¹-(4-methoxyphenyl)-*N*²-phenylpropane-1,2-diamine (**III-105**) with 59 mg (48 μl , 0.275 mmol) of 4-bromo-*tert*-butylbenzene was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ^1H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 49 mg (50%) of the title compound as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.38 (t, $J = 8.4$ Hz, 2 H), 7.30 (d, $J = 8.0$ Hz, 2 H), 7.19 (d, $J = 7.6$ Hz, 2 H), 7.07 (d, $J = 8.0$ Hz, 3 H), 6.92–6.89 (m, 2 H), 6.87–6.84 (m, 2 H), 3.78 (s, 3 H), 3.68–3.57 (m, 2 H), 3.26 (dd, $J = 3.2, 11.2$ Hz, 1 H), 3.09 (dd, $J = 3.2, 12.0$ Hz, 1 H), 3.00–2.93 (m, 2 H), 2.71–2.58 (m, 2 H), 1.31 (s, 9 H), 1.09 (d, $J = 6$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.2, 149.1, 148.7, 146.2, 136.6, 129.5, 129.0, 125.5, 122.5, 121.7, 119.0, 114.6, 59.8, 58.4, 55.8, 54.6, 53.4, 38.0, 34.6, 31.6, 18.6; IR (film) 2961, 1596, 1510 cm^{-1} . MS (ESI) 429.2901 (429.2906 calcd for $\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}$, $\text{M} + \text{H}^+$).

Synthesis of 2,3-Disubstituted Piperazines

***tert*-butyl 2-(benzyl(but-3-en-2-yl)amino)ethylcarbamate (III-136).** General procedure 3 was used for the coupling of 2-(*tert*-butoxycarbonylamino)acetic acid (6.95 g, 39.70 mmol) and *N*-benzylbut-3-en-2-amine (6.40 g, 39.7 mmol) using 1.40 eq of DCC instead of 2 eq. This procedure afforded 10.73 g (85%) of *tert*-butyl 2-(benzyl(but-3-en-2-

yl)amino)-2-oxoethylcarbamate (**III-134**) as a white solid, which was contaminated with ca. 15% of dicyclohexylurea and was observed as a 1.2:1 mixture of rotamers. ^1H NMR (400 MHz, CDCl_3) δ 7.37–7.27 (m, 2.27 H), 7.23–7.16 (m, 2.73 H), 5.89–5.67 (m, 1 H), 5.65–5.58 (m, 1 H), 5.54–5.44 (m, 1 H), 5.31–5.06 (m, 2 H), 4.78 (d, $J = 15.6$ Hz, 0.40 H), 4.41 (d, $J = 12.4$ Hz, 1.1 H), 4.28 (d, $J = 15.6$ Hz, 0.50 H), 4.19–4.00 (m, 1 H), 3.96–3.66 (m, 1 H), 1.45 (s, 4.9 H), 1.41 (s, 4.1 H), 1.23 (d, $J = 7.2$ Hz, 3 H).

The *tert*-butyl 2-(benzyl(but-3-en-2-yl)amino)-2-oxoethylcarbamate (**III-134**) coupling product of the DCC reaction (5.14 g, 16.14 mmol) was reduced with lithium aluminum hydride following general procedure 3. This procedure afforded 2.50 g (51%) of the title compound as a yellow solid, m. p. 38–40 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.31–7.24 (m, 4 H), 7.24–7.21 (m, 1 H), 5.90–5.81 (m, 1 H), 5.17–5.05 (m, 2 H), 4.84 (s, 1 H), 3.63–3.52 (m, 2 H), 3.30 (t, $J = 6.4$ Hz, 1 H), 3.12–3.06 (m, 2 H), 2.64–2.57 (m, 1 H), 2.54–2.48 (m, 1 H), 1.44 (s, 9 H), 1.14 (d, $J = 6.4$ Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 156.1, 140.5, 139.5, 128.6, 128.4, 126.9, 115.9, 78.8, 56.7, 54.6, 49.0, 38.7, 28.5, 15.4; IR (film) 3425, 3365, 2974, 1714 cm^{-1} . MS (ESI) 327.2035 (327.2048 calcd for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_2$, $\text{M} + \text{Na}^+$).

4-(2-(benzyl(but-3-en-2-yl)amino)ethylamino)benzotrile (III-140). General procedure 4 was used for the deprotection of **III-136** (1.35 g, 4.44 mmol). This procedure afforded 842 mg (93%) of N^1 -benzyl- N^1 -(but-3-en-2-yl)ethane-1,2-diamine (**III-138**) as a yellow oil. The crude product was immediately subjected to the subsequent reaction without further purification. ^1H NMR (300 MHz, CDCl_3) δ 7.39–7.19 (m, 5 H), 5.94–

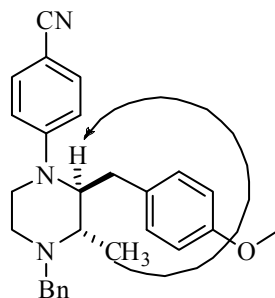
5.82 (m, 1 H), 5.16–5.03 (m, 2 H), 3.65–3.53 (m, 2 H), 3.34–3.25 (m, 1 H), 2.72–2.61 (m, 2 H), 2.60–2.44 (m, 2 H), 1.21 (broad s, 2 H), 1.14 (d, $J = 6.9$ Hz, 3 H).

General procedure 4 was used for the *N*-arylation of *N*¹-benzyl-*N*¹-(but-3-en-2-yl)ethane-1,2-diamine (**III-138**) (681 mg, 3.33 mmol) with 4-bromobenzonitrile (606 mg, 3.33 mmol). This procedure afforded 905 mg (89%) of the title compound as a yellow-orange oil. ¹H NMR (300 MHz, CDCl₃) δ 7.43–7.21 (m, 7 H), 6.41 (d, $J = 9$ Hz, 2 H), 5.94–5.83 (m, 1 H), 5.21–5.08 (m, 2 H), 4.65 (s, 1 H), 3.66–3.52 (m, 2 H), 3.39–3.30 (m, 1 H), 3.08–2.97 (m, 2 H), 2.82–2.63 (m, 2 H), 1.20 (d, $J = 6.6$ Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 151.5, 140.2, 139.2, 133.5, 128.6, 128.4, 127.1, 120.7, 116.2, 112.2, 97.8, 56.8, 54.3, 47.8, 40.7, 15.3; IR (film) 3380, 2968, 2212, 1608 cm⁻¹. MS (ESI) 306.1975 (306.1970 calcd for C₂₀H₂₃N₃, M + H⁺).

4-((2*S*,3*S*)-4-benzyl-2-(4-methoxybenzyl)-3-methylpiperazin-1-yl)benzonitrile (III-142). The reaction of 100 mg (0.327 mmol) of 4-(2-(benzyl(but-3-en-2-yl)amino)ethylamino)benzonitrile (**III-140**) with 61 mg (50 μl, 0.392 mmol) of 4-bromoanisole was conducted for 10 h according to the general procedure except xylenes was used in place of toluene and the reaction was conducted at 140 °C. The product was formed with 3:1 dr as judged by ¹H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 102 mg (76%) of the title compound was obtained as an orange solid, m.p. 118–125 °C. The diastereomers were subsequently separated by careful flash chromatography on silica gel.

Major (*trans*) diastereomer (**III-142**): ^1H NMR (400 MHz, CDCl_3) δ 7.41–7.29 (m, 5 H), 7.24 (d, $J = 8.8$ Hz, 2 H), 6.97 (d, $J = 8.4$ Hz, 2 H), 6.65 (d, $J = 6.8$ Hz, 2 H), 6.48 (d, $J = 9.2$ Hz, 2 H), 4.16 (d, $J = 13.2$ Hz, 1 H), 4.06–4.02 (m, 1 H), 3.71 (s, 3 H), 3.42–3.39 (m, 2 H), 3.20–3.14 (m, 1 H), 3.03–2.96 (m, 2 H), 2.81 (dt, $J = 2.8, 11.2$ Hz, 1 H), 2.70–2.66 (m, 1 H), 2.15–2.08 (m, 1 H), 1.28 (d, $J = 6.4$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.1, 152.9, 139.5, 133.8, 133.3, 131.4, 130.5, 129.0, 128.5, 127.2, 120.6, 113.8, 98.0, 63.2, 60.2, 57.8, 55.4, 52.2, 41.8, 30.5, 18.8; IR (film) 2953, 2212, 1602 cm^{-1} . MS (ESI) 412.2370 (412.2389 calcd for $\text{C}_{27}\text{H}_{29}\text{N}_3\text{O}$, $\text{M} + \text{H}^+$).

Minor (*cis*) diastereomer (**III-142b**): orange solid, m.p. 92–98 °C, isolated in combination with a 5-10% unidentified minor impurity. ^1H NMR (400 MHz, CDCl_3) δ 7.49 (d, $J = 8.8$ Hz, 2 H), 7.46–7.44 (m, 2 H), 7.39 (t, $J = 6.8$ Hz, 1 H), 7.35–7.31 (m, 2 H), 6.91 (d, $J = 8.4$ Hz, 2 H), 6.84 (d, $J = 9.2$ Hz, 2 H), 6.72 (d, $J = 8.8$ Hz, 2 H), 3.76 (s, 3 H), 3.72–3.55 (m, 2 H), 3.49–3.41 (m, 1 H), 3.36–3.26 (m, 2 H), 3.02–2.97 (m, 1 H), 2.82–2.74 (m, 1 H), 2.72–2.63 (m, 2 H), 2.56 (dd, $J = 3.6, 12.8$ Hz, 1 H), 1.04 (d, $J = 6.4$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.2, 153.7, 139.2, 133.8, 131.5, 130.4, 129.2, 129.0, 128.6, 127.4, 120.5, 114.0, 99.1, 63.3, 59.0, 55.4, 51.4, 44.3, 42.3, 33.2, 9.1; IR (film) 2917, 2214, 1604 cm^{-1} . MS (ESI) 412.2379 (412.2389 calcd for $\text{C}_{27}\text{H}_{29}\text{N}_3\text{O}$, $\text{M} + \text{H}^+$). Noesy-2D experiments on the minor diastereomer revealed a *trans*-relationship as shown below.



(2*R*,3*R*)-1-benzyl-3-(4-*tert*-butylbenzyl)-2-cyclohexyl-4-phenylpiperazine (III-143).

The reaction of 50 mg (0.144 mmol) of **(III-141)** with 37 mg (0.173 mmol) of 4-bromo-*tert*-butylbenzene was conducted for 10 h according to the general procedure (Toluene, 105 °C). The product was formed with 2:1 dr as judged by ¹H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 35 mg (51%) of the title compound was obtained. The diastereomers were not separable by column chromatography greater than a 1.3:1 mixture. Data are for the mixture: ¹H NMR (400 MHz, CDCl₃) δ 7.48–6.56 (m, 32 H), 4.25–3.89 (m, 6.9 H), 3.74–3.55 (m, 4.6 H), 3.32–2.50 (m, 11.5 H), 2.08–1.46 (m, 23 H), 1.31 (s, 9 H), 1.27 (s, 7 H).

***tert*-butyl 2-(benzyl(cyclopent-2-enyl)amino)ethylcarbamate (III-151).** General procedure 3 was used for the coupling of *N*-Boc glycine (**(III-26)**) (1.25 g, 7.16 mmol) with *N*-benzylcyclopent-2-enamine (1.25 g, 7.16 mmol) with the only difference being the use of DCC as a 3 M solution (the amount of CH₂Cl₂ was adjusted appropriately to provide a 0.5 M solution). This procedure afforded 1.81 g (77%) of *tert*-butyl 2-(benzyl(cyclopent-2-enyl)amino)-2-oxoethylcarbamate (**(III-150)**) as a white solid, which was contaminated with ca. 15% dicyclohexylurea. This material was carried on without further purification. This molecule was isolated as a 1.4:1 mixture of rotamers; data are

for the mixture. ^1H NMR (500 MHz, CDCl_3) δ 7.34–7.31 (m, 1 H), 7.29–7.27 (m, 1 H), 7.22–7.13 (m, 3 H), 5.98–5.95 (m, 1 H), 5.80–5.74 (m, 0.58 H), 5.65 (s, 0.42 H), 5.54–5.52 (m, 0.42 H), 5.51–5.49 (m, 1 H), 4.96–4.93 (m, 0.58 H), 4.58–4.50 (m, 1 H), 4.42–4.38 (m, 1 H), 4.22–4.09 (m, 1 H), 4.02–4.01 (m, 0.5 H), 3.91–3.87 (m, 0.5 H), 3.77–3.73 (m, 1 H), 2.41–2.22 (m, 3 H), 1.45 (s, (5.2 H), 1.41 (s, 3.8 H).

The *tert*-butyl 2-(benzyl(cyclopent-2-enyl)amino)-2-oxoethylcarbamate product (**III-150**) of the DCC coupling reaction (1.81 g, 5.48 mmol) was reduced following general procedure 3. This procedure afforded 1.21 g (70%) of the title compound as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.32–7.26 (m, 4 H), 7.25–7.21 (m, 1 H), 5.90–5.88 (m, 1 H), 5.71–5.68 (m, 1 H), 4.84 (s, 1 H), 4.06–4.05 (m, 1 H), 3.64 (d, $J = 13.6$ Hz, 1 H), 3.44 (d, $J = 14$ Hz, 1 H), 3.16–3.07 (m, 2 H), 2.60–2.50 (m, 1 H), 2.49–2.44 (m, 1 H), 2.40–2.22 (m, 2 H), 1.97–1.88 (m, 1 H), 1.74–1.59 (m, 1 H), 1.43 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.2, 140.5, 133.7, 131.9, 128.8, 128.4, 127.0, 79.0, 67.3, 55.4, 49.6, 38.6, 31.8, 28.6, 23.8; IR (film) 3367, 2975, 1715 cm^{-1} . MS (ESI) 317.2220 (317.2229 calcd for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_2$, $\text{M} + \text{H}^+$).

***N*¹-benzyl-*N*¹-(cyclopent-2-enyl)-*N*²-phenylethane-1,2-diamine (III-153)**. General procedure 4 was used for the deprotection of *tert*-butyl 2-(benzyl(cyclopent-2-enyl)amino)ethylcarbamate (**III-151**) (1.20 g, 3.79 mmol). This procedure afforded 754 mg (92%) of *N*¹-benzyl-*N*¹-(cyclopent-2-enyl)ethane-1,2-diamine (**III-152**) as a yellow oil. The crude product was immediately subjected to the subsequent reaction without further purification. ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.28 (m, 4 H), 7.25–7.21 (m, 1

H), 5.90–5.87 (m, 1 H) 5.73–5.70 (m, 1 H), 4.08–4.04 (m, 1 H), 3.66 (d, $J = 14$ Hz, 1 H), 3.46 (d, $J = 14$ Hz, 1 H), 2.73–2.61 (m, 2 H), 2.56–2.42 (m, 2 H), 2.41–2.23 (m, 2 H), 1.97–1.88 (m, 1 H), 1.78–1.69 (m, 1 H), 1.31 (s, 2 H).

General procedure 4 was used for the *N*-arylation of *N*¹-benzyl-*N*¹-(cyclopent-2-enyl)ethane-1,2-diamine (**III-152**) (754 mg, 3.48 mmol) with bromobenzene (367 μ l, 3.48 mmol). This procedure afforded 507 mg (50%) of the title compound as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.34–7.29 (m, 4 H), 7.25–7.21 (m, 1 H), 7.16–7.12 (m, 2 H), 6.67 (td, $J = 1.0, 7.5$ Hz, 1 H), 6.54 (dd, $J = 1.0, 8.5$ Hz, 2 H), 5.91–5.88 (m, 1 H), 5.73–5.71 (m, 1 H), 4.16 (s, 1 H), 4.11–4.08 (m, 1 H), 3.67 (d, $J = 13.5$ Hz, 1 H), 3.46 (d, $J = 13.5$ Hz, 1 H), 3.12–3.04 (m, 2 H), 2.78–2.73 (m, 1 H), 2.67–2.63 (m, 1 H), 2.41–2.33 (m, 1 H), 2.32–2.24 (m, 1 H), 1.98–1.91 (m, 1 H), 1.79–1.72 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 148.8, 140.6, 133.8, 131.9, 129.3, 128.9, 128.5, 127.1, 117.2, 113.1, 67.3, 55.3, 49.0, 41.8, 31.9, 23.9; IR (film) 3392, 2943, 1602 cm⁻¹. MS (ES) 293.2012 (293.2018 calcd for C₂₀H₂₄N₂, M + H⁺).

(4-(1-benzyl-4-phenyloctahydro-1H-cyclopenta[b]pyrazin-5yl)phenyl)(phenyl)

methanone (III-154). A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with 6.30 mg Pd₂(dba)₃ (2 mol % complex, 4 mol % Pd, 0.00684 mmol), 12.7 mg P(2-furyl)₃ (16 mol %, 0.0547 mmol), 40 mg sodium *tert*-butoxide (0.410 mmol, 1.2 equiv), and 114 mg of 4-bromobenzophenone (0.410 mmol, 1.2 equiv). The Schlenk tube was purged with nitrogen and 100 mg of *N*¹-benzyl-*N*¹-(cyclopent-2-enyl)-*N*²phenylethane-1,2-diamine (**III-153**) was added as a

solution in xylenes (2.5 mL/0.5 mmol substrate). The Schlenk tube was then heated to 135 °C with stirring until the starting material has been consumed as judged by ¹H NMR analysis of an aliquot taken from the reaction mixture. The reaction mixture was then cooled to room temperature, saturated aqueous ammonium chloride (2–3 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel afforded 104 mg (64%) of the title compound as a solid, m.p. 147–150 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, *J* = 7.2 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.81–7.76 (m, 2 H), 7.72 (m, *J* = 7.6 Hz, 1 H), 7.62–7.43 (m, 5 H), 7.39–7.28 (m, 5 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 6.68 (t, *J* = 7.2 Hz, 1 H), 6.62 (d, *J* = 8.4 Hz, 2 H), 4.59–4.56 (m, 1 H), 4.27 (d, *J* = 13.6 Hz, 1 H), 3.86–3.80 (m, 1 H), 2.92 (d, *J* = 13.6 Hz, 2 H), 2.86 (t, *J* = 5.2 Hz, 1 H), 2.76 (d, *J* = 11.6 Hz, 1 H), 2.47–2.32 (m, 3 H), 2.30–2.17 (m, 2 H), 2.03–1.96 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 196.9, 149.0, 148.4, 139.1, 138.2, 135.3, 132.3, 130.9, 130.2, 129.32, 129.27, 129.0, 128.6, 128.3, 127.2, 116.9, 112.8, 64.6, 61.8, 59.2, 51.2, 44.8, 43.5, 29.7, 28.8; IR (film) 3027, 2945, 1652, 1598 cm⁻¹. MS (ESI) 473.2591 (473.2593 calcd for C₃₃H₃₂N₂O, M + H⁺).

4-(1-benzyl-4-phenyloctahydro-1H-cyclopenta[b]pyrazin-5-yl)benzotrile (III-155).

A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with 6.30 mg Pd₂(dba)₃ (2 mol % complex, 4 mol % Pd, 0.00684 mmol), 12.7 mg P(2-furyl)₃ (16 mol %, 0.0547 mmol), 40 mg sodium *tert*-butoxide (0.410 mmol, 1.2 equiv), and 75 mg of 4-bromobenzotrile (0.410 mmol, 1.2 equiv).

The Schlenk tube was purged with nitrogen and 100 mg of *N*¹-benzyl-*N*¹-(cyclopent-2-enyl)-*N*²-phenylethane-1,2-diamine (**III-153**) was added as a solution in xylenes (2.5 mL/0.5 mmol substrate). The Schlenk tube was then heated to 135 °C with stirring until the starting material has been consumed as judged by ¹H NMR analysis of an aliquot taken from the reaction mixture. The reaction mixture was then cooled to room temperature, saturated aqueous ammonium chloride (2–3 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel afforded 68 mg (51%) of the title compound as a solid, m.p. 145–149 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.30 (m, 9 H), 7.20–7.16 (m, 2 H), 6.70 (t, *J* = 7.6 Hz, 1 H), 6.59 (d, *J* = 8.0 Hz, 2 H), 4.57–4.53 (m, 1 H), 4.25 (d, *J* = 13.6 Hz, 1 H), 3.82–3.76 (m, 1 H), 2.92 (d, *J* = 14 Hz, 1H), 2.89–2.88 (m, 1 H), 2.85 (t, *J* = 5.2 Hz, 1 H), 2.78–2.74 (m, 1 H), 2.41–2.31 (m, 2 H), 2.27–2.13 (m, 2 H), 2.03–1.92 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 149.0, 148.7, 138.8, 131.7, 130.7, 129.4, 129.0, 128.6, 127.3, 119.5, 117.1, 112.7, 109.6, 64.6, 61.7, 59.2, 51.1, 44.9, 43.4, 29.7, 28.7; IR (film) 3060, 2947, 2225, 1597 cm⁻¹. MS (ESI) 394.2272 (394.2283 calcd for C₂₇H₂₇N₃, M + H⁺).

***N*¹-allylbenzene-1,2-diamine (III-157)**. The synthesis of the title compound was achieved on a 30.0 g scale according to the published procedure which afforded 11.0 g of a purple oil (54%). ¹H NMR (500 MHz, CDCl₃) δ 6.82 (td, *J* = 1.5, 7.5 Hz, 1 H), 6.74–6.66 (m, 3 H), 6.06–5.99 (m, 1 H), 5.33–5.29 (m, 1 H), 5.20–5.17 (m, 1 H), 3.78 (d, 2 H), 3.46 (s, 1 H), 3.34 (s, 2 H).

General Procedure 5: *N*-arylation reactions to afford *N*-allyl phenylenediamines substrates (Scheme 36)

A flame-dried Schlenk tube equipped with a magnetic stirbar was charged with Pd₂(dba)₃ (1 mol % complex, 2 mol % Pd), *Pt*-Bu₂(*o*-biphenyl) (2 mol %), sodium *tert*-butoxide (1.2 equiv), the appropriate aryl bromide (1.0 equiv), and a 0.5 M solution of the primary amine (1.0 equiv) in toluene. The reaction mixture was heated to 80 °C with stirring until the starting material had been consumed as judged by TLC analysis (ca. 6 h). The mixture was cooled to rt and a solution of aqueous ammonium chloride was added (4 mL). The resulting mixture was extracted with ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

***N*¹-allyl-*N*²-phenylbenzene-1,2-diamine (III-158).** General procedure 5 was used for the *N*-arylation of *N*¹-allylbenzene-1,2-diamine (III-157) (300 mg, 2.02 mmol) with 318 mg of bromobenzene (232 μ l, 2.20 mmol, 1.09 eq). This procedure afforded 313 mg (69%) of the title compound as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.23–7.19 (m, 2 H), 7.14–7.09 (m, 2 H), 6.82 (t, *J* = 7.2 Hz, 1 H), 6.74–6.69 (m, 4 H), 5.96–5.90 (m, 1 H), 5.26–5.21 (m, 1 H), 5.16–5.12 (m, 1 H), 5.09 (s, 1 H), 4.33 (s, 1 H), 3.81–3.78 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 146.0, 144.1, 135.6, 129.5, 128.3, 126.4, 125.2, 119.4, 117.5, 116.2, 115.4, 111.5, 46.4; IR (film) 3370, 3045, 1598 cm⁻¹. MS (ESI) 225.1383 (225.1392 calcd for C₁₅H₁₆N₂, M + H⁺).

4-(2-(allylamino)phenylamino)benzotrile (III-159). General procedure 5 was used for the *N*-arylation of *N*¹-allylbenzene-1,2-diamine (**III-157**) (300 mg, 2.02 mmol) with 368 mg of 4-bromobenzotrile (2.02 mmol). This procedure afforded 362 mg (72%) of the title compound as a orange oil. ¹H NMR (300 MHz, CDCl₃) δ 7.44 (d, *J* = 8.4 Hz, 2 H), 7.19 (t, *J* = 8.4 Hz, 1 H), 7.10 (d, *J* = 7.2 Hz, 1 H), 6.74 (d, *J* = 7.5 Hz, 2 H), 6.66 (d, *J* = 9 Hz, 2 H), 5.96–5.84 (m, 1 H), 5.50 (s, 1 H), 5.26–5.15 (m, 2 H), 4.18 (s, 1 H), 3.78 (t, *J* = 12 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 150.0, 144.7, 135.2, 133.9, 128.3, 127.1, 125.0, 120.3, 117.6, 116.5, 114.3, 111.9, 100.9, 46.2; IR (film) 3338, 1609 cm⁻¹. MS (ESI) 250.1335 (250.1344 calcd for C₁₆H₁₅N₃, M + H⁺).

***N*¹-allyl-*N*²-(4-methoxyphenyl)benzene-1,2-diamine (III-160).** General procedure 5 was used for the *N*-arylation of *N*¹-allylbenzene-1,2-diamine (**III-157**) (300 mg, 2.02 mmol) with 378 mg of 4-bromoanisole (254 μl, 2.02 mmol). This procedure afforded 387 mg (75%) of the title compound as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.07 (d, *J* = 7.6 Hz, 2 H), 6.86–6.82 (m, 2 H), 6.80–6.71 (m, 4 H), 6.03–5.93 (m, 1 H), 5.31–5.26 (m, 1 H), 5.20–5.17 (m, 1 H), 4.95 (s, 1 H), 4.26 (s, 1 H), 3.82 (dd, *J* = 4.8 Hz, 2 H), 3.80 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 153.8, 142.8, 139.0, 135.6, 130.4, 125.0, 122.8, 118.0, 117.7, 116.2, 114.9, 111.6, 55.8, 46.5; IR (film) 3367, 1508 cm⁻¹. MS (ESI) 255.1487 (255.1497 calcd for C₁₆H₁₈N₂O, M + H⁺).

General Procedure 6: Synthesis of Benzopiperazines via Coupling with Aryl Bromides (Table 15). A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with Pd₂(dba)₃ (1 mol % complex, 2 mol % Pd), BINAP (2 mol %), sodium *tert*-butoxide (1.2 equiv), and the aryl bromide (1.0

equiv) unless otherwise noted. The Schlenk tube was purged with nitrogen and the amine was added as a solution in toluene (2.5 mL/0.5 mmol substrate). The Schlenk tube was then heated to 105 °C with stirring until the starting material has been consumed as judged by ¹H NMR analysis of an aliquot taken from the reaction mixture. The reaction mixture was then cooled to room temperature, saturated aqueous ammonium chloride (2–3 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

2-((1-benzyl-1H-indol-5-yl)methyl)-1-phenyl-1,2,3,4-tetrahydroquinoxaline (III-161). General procedure 6 was used for the coupling of 77 mg (0.344 mmol) of *N*¹-allyl-*N*²-phenylbenzene-1,2-diamine (**III-158**) with 98.3 mg (0.344 mmol) of 1-benzyl-5-bromo-1H-indole was conducted for 10 h according to the general procedure. Upon purification, 70 mg (62%) of the title compound was obtained as an orange solid, m.p. 60–65 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.50 (s, 1 H), 7.30–7.23 (m, 3 H), 7.19 (d, *J* = 8.5 Hz, 1 H), 7.11–7.08 (m, 3 H), 7.06–7.01 (m, 4 H), 6.95–6.86 (m, 2 H), 6.78–6.72 (m, 1 H), 6.48 (d, *J* = 3 Hz, 1 H), 5.30 (s, 2 H), 4.06–4.00 (m, 1 H), 3.32–3.26 (m, 2 H), 3.11–3.07 (m, 1 H), 2.97–2.93 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 149.2, 137.8, 135.5, 135.4, 130.6, 129.7, 129.3, 129.2, 128.9, 128.6, 127.7, 126.9, 123.7, 122.8, 122.1, 121.6, 120.9, 120.2, 118.2, 115.2, 109.8, 101.5, 60.4, 50.3, 41.8, 38.0; IR (film) 3408, 2916, 1589 cm⁻¹. MS (ESI) 430.2279 (430.2283 calcd for C₃₀H₂₇N₃, M + H⁺).

2-(4-methoxybenzyl)-1-phenyl-1,2,3,4-tetrahydroquinoxaline (III-162). General procedure 6 was used for the coupling of 77 mg (0.344 mmol) of *N*¹-allyl-*N*²-phenylbenzene-1,2-diamine (**III-158**) with 64.3 mg (44 μ L, 0.344 mmol) of 4-bromoanisole was conducted for 10 h according to the general procedure. Upon purification, 70 mg (62%) of the title compound was obtained as an orange oil. ¹H NMR (300 MHz, CDCl₃) δ 7.23–7.12 (m, 4 H), 6.94–6.90 (m, 4 H), 6.87–6.76 (m, 3 H), 6.69–6.60 (m, 2 H), 3.92–3.87 (m, 2 H), 3.80 (s, 3 H), 3.28–3.15 (m, 2 H), 2.95–2.88 (m, 1 H), 2.78–2.71 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 158.3, 149.5, 135.6, 131.7, 130.6, 129.4, 129.3, 122.7, 122.2, 121.2, 120.8, 118.3, 115.2, 114.0, 60.2, 55.4, 42.0, 37.1; IR (film) 3407, 2954, 1589 cm⁻¹. MS (ESI) 331.1795 (331.1810 calcd for C₂₂H₂₂N₂O, M + H⁺).

2-(4-methoxybenzyl)-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoxaline (III-164). General procedure 6 was used for the coupling of 82 mg (0.322 mmol) of *N*¹-allyl-*N*²-(4-methoxyphenyl)benzene-1,2-diamine (**III-160**) with 60.2 mg (41 μ L, 0.322 mmol) of 4-bromoanisole was conducted for 10 h according to the general procedure. Upon purification, 60 mg (52%) of the title compound was obtained as an orange oil. ¹H NMR (300 MHz, CDCl₃) δ 7.10 (d, *J* = 9 Hz, 3 H), 6.94–6.92 (m, 2 H), 6.84–6.75 (m, 4 H), 6.71–6.57 (m, 3 H), 3.84–3.73 (m, 8 H), 3.20 (qd, *J* = 3.5, 11 Hz, 2 H), 2.93–2.89 (m, 1 H), 2.77–2.73 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 158.3, 156.1, 142.2, 134.9, 132.0, 131.7, 130.6, 126.5, 119.7, 118.8, 118.5, 115.0, 114.8, 114.0, 61.3, 55.7, 55.5, 41.9, 37.4; IR (film) 3394, 2952, 1507 cm⁻¹. MS (ESI) 361.1914 (361.1916 calcd for C₂₃H₂₄N₂O₂, M + H⁺).

4-(2-benzyl-3,4-dihydroquinoxalin-1(2H)-yl)benzonitrile (III-163). General procedure 6 was used for the coupling of 150 mg (0.602 mmol) of 4-(2-(allylamino)phenylamino)benzonitrile (**III-159**) with 104 mg (70 μ L, 0.662 mmol, 1.10 eq) of bromobenzene was conducted for 10 h according to the general procedure. Upon purification, 125 mg (64%) of the title compound was obtained as an orange solid, m.p. 55–60 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.35–7.30 (m, 4 H), 7.27–7.24 (m, 2 H), 7.22–7.20 (m, 2 H), 7.08–7.06 (m, 1 H), 6.94–6.91 (m, 1 H), 6.78–6.75 (m, 2 H), 6.72–6.67 (m, 1 H), 4.07 (s, 1 H), 4.05–4.01 (m, 1 H), 3.36–3.28 (m, 2 H), 2.96–2.91 (m, 1 H), 2.79–2.75 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.2, 139.1, 136.5, 133.3, 129.5, 128.8, 126.8, 125.1, 124.0, 122.7, 119.9, 119.3, 118.0, 115.5, 102.3, 58.3, 43.4, 37.3; IR (film) 3400, 2216, 1597 cm^{-1} . MS (ESI) 326.1646 (326.1657 calcd for $\text{C}_{22}\text{H}_{19}\text{N}_3$, $\text{M} + \text{H}^+$).

References

- ¹ Reproduced in part with permission from Nakhla, J. S.; Wolfe, J. P. "A Concise Asymmetric Synthesis of *cis*-2,6-Disubstituted *N*-Aryl Piperazines via Pd-Catalyzed Carboamination Reactions" *Org. Lett.* **2007**, *9*, 3279–3282. Copyright 2007 American Chemical Society.
- ² There are both bioactive piperazine pharmaceuticals and natural products. For recent syntheses of natural products in the druggable family, which are highly bioactive natural products, see: (a) Kawasaki, T.; Enoki, H.; Matsumura, K.; Ohyama, M.; Inagawa, M.; Sakamoto, M. *Org. Lett.* **2000**, *2*, 3027. (b) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 3185.
- ³ Nilsson, J. W.; Thorstensson, F.; Kvarnström, I.; Oprea, T.; Samuelsson, B.; Nilsson, I. *J. Comb. Chem.* **2001**, *3*, 546–553.
- ⁴ Brioni, J. D.; Moreland, R. B.; Cowart, M.; Hsieh, G. C.; Stewart, A. O.; Hedlund, P.; Donnelly-Roberts, D.L.; Nakane, M.; Lynch, J. J.; Kolasa, T.; Polakowski, J. S.; Osinski, M. A.; Marsh, K.; Andersson, K. E.; Sullivan, J. P. *Proc. Natl. Acad. Sci. USA.* **2004**, *101*, 6758–6763.
- ⁵ Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, O. M.; Roth, E.; Sardana, V. V.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotlib, L.; Holloway, M. K.; Lin, J.; Chen, I.-W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. L-735,524: An Orally Bioavailable Human Immunodeficiency Virus Type 1 Protease Inhibitor. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4096-4100. (b) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443.
- ⁶ Liddle, J.; Allen, M. J.; Borthwick, A. D.; Brooks, D. P.; Davies, D. E.; Edwards, R. M.; Exall, A. M.; Hamlett, C.; Irving, W. R.; Mason, A. M.; McCafferty, G. P.; Nerozzi, F.; Peace, S.; Philp, J.; Pollard, D.; Pullen, M. A.; Shabbir, S. S.; Sollis, S. L.; Westfall, T. D.; Woollard, P. M.; Wu, C.; Hickey, D. M. B. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 90–94.
- ⁷ Aicher, T. D.; Chen, Z.; Krushinski, J. H.; Huerou, Y. L.; Pineiro-Nunez, M. M.; Ruley, K. M.; Schaus, J. M.; Thompson, D. C.; Tupper, D. E.; Chen, Y.; Faul, M. M.; Rocco, V. P. "Piperazine Substituted Aryl Benzodiazepines and their use as Dopamine Receptor Antagonists for the Treatment of Psychotic Disorders." US Patent Number: 7, 214, 673, B2. Date of Patent: May 8, 2007.
- ⁸ For examples of biologically active 2,6-disubstituted piperazines, see: (a) Zheng, G.; Dwoskin, L. P.; Deaciuc, A. G.; Zhu, J.; Jones, M. D.; Crooks, P. A. *Bioorg. Med. Chem.* **2005**, *13*, 3899–3909. (b) Chu-Moyer, M. Y.; Ballinger, W. E.; Beebe, D. A.; Berger, R.;

Coutcher, J. B.; Day, W. W.; Li, J.; Mylari, B. L.; Oates, P. J.; Weekly, R. M. *J. Med. Chem.* **2002**, *45*, 511–528.

⁹ (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930. (b) Dinsmore, C. J.; Beshore, D. C. *Tetrahedron* **2002**, *58*, 3297–3312. (c) Jung, M. E.; Rohloff, J. C. *J. Org. Chem.* **1985**, *50*, 4909–4913.

¹⁰ For syntheses of nonracemic 2,6-dialkylpiperazines, see: (a) Schanen, V.; Cherrier, M.-P.; de Melo, S. J.; Quirion, J.-C.; Husson, H.-P. *Synthesis* **1996**, 833–837. (b) Mickelson, J. W.; Belonga, K. L.; Jacobsen, E. J. *J. Org. Chem.* **1995**, *60*, 4177–4183. (c) Mickelson, J. W.; Jacobsen, E. J. *Tetrahedron: Asymmetry* **1995**, *6*, 19–22.

¹¹ For syntheses of racemic 2,6-dialkylpiperazines, see: (a) Berkheij, M.; van der Sluis, L.; Sewing, C.; den Boer, D. J.; Terpstra, J. W.; Hiemstra, H.; Bakker, W. I. I.; van den Hoogenband, A.; van Maarseveen, J. H. *Tetrahedron Lett.* **2005**, *46*, 2369–2371. (b) Mouhtaram, M.; Jung, L.; Stambach, J. F. *Tetrahedron* **1993**, *49*, 1391–1400.

¹² For selected recent approaches to the synthesis of substituted piperazine derivatives, see: (a) Mercer, G. J.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 1591–1594. (b) Ferber, B.; Prestat, G.; Vogel, S.; Madec, D.; Poli, G. *Synlett* **2006**, 2133. (c) Viso, A.; Fernandez de la Pradilla, R.; Flores, A.; Garcia, A.; Tortosa, M.; Lopez-Rodriguez, M. L. *J. Org. Chem.* **2006**, *71*, 1442–1448 and references cited therein.

¹³ (a) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605–3608. (b) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906–13907. (c) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447–6459. (d) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644–8651. (e) Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575–2578. (f) Ney, J. E.; Hay, M. B.; Yang, Q.; Wolfe, J. P. *Adv. Synth. Catal.* **2005**, *347*, 1614–1620. (g) Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353–2356. (h) Dongol, K. G.; Tay, B. Y. *Tetrahedron Lett.* **2006**, *47*, 927–930. (i) Bertand, M. B.; Leathen, M. L.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 457–460. (j) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571–582. (k) Peng, J.; Lin, W.; Yuan, S.; Chen, Y. *J. Org. Chem.* **2007**, *72*, 3145–3148.

¹⁴ For examples of Cu-catalyzed intramolecular carboamination, see: (a) Sherman, E. S.; Fuller, P. H.; Kasi, D.; Chemler, S. R. *J. Org. Chem.* **2007**, *72*, 3896–3905. (b) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573–1575. For Pd(II)-catalyzed alkoxyacylation of alkenes bearing tethered nitrogen nucleophiles, see: (c) Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1997**, *62*, 2113–2122. For carboamination reactions between alkenes and *N*-allylsulfonamides, see: (d) Scarborough, C. C.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 3251–3254. For carboamination of vinylcyclopropanes, see: (e) Larock, R. C.; Yum, E. K. *Synlett* **1990**, 529–530. For 1,1-carboamination of alkenes, see: (f) Larock, R. C.; Yang, H.; Weinreb, S. M.; Herr, R. J. *J. Org. Chem.* **1994**, *59*, 4172–4178.

¹⁵ Chiral amino acids are known to racemize under strongly basic conditions and or under high temperature, see reference 16 and references therein.

- ¹⁶ Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459–12467.
- ¹⁷ Lu, Z.; Twieg, R. J. *Tetrahedron Lett.* **2005**, *46*, 2997–3001.
- ¹⁸ DEPBT = 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one. See: Li, H.; Jiang, X.; Ye, Y.-h.; Fan, C.; Romoff, T.; Goodman, M. *Org. Lett.* **1999**, *1*, 91–94.
- ¹⁹ Cu-catalyzed *N*-arylation reactions of alanine afforded products with $\leq 93\%$ ee. See reference 10.
- ²⁰ (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209. (b) Hartwig, J. F. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley, VCH: Weinheim, Germany, 2002; p 107. (c) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626.
- ²¹ The ligand dppb was also used in the cyclization of glycine derivative diamines for the synthesis of monosubstituted piperazines (see eq 23-24).
- ²² Fritz, J. A.; Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2531–2534.
- ²³ The catalyst optimization was carried out with an excess phosphine: metal ratio and these are the numbers indicated in the table.
- ²⁴ The minor diastereomer was not observed in reactions of phenylalanine derivatives.
- ²⁵ Enantiopurity of all products was measured by chiral HPLC analysis.
- ²⁶ Initial studies on carboaminations of amides such as **III-44** or **III-45** suggest these transformations may be feasible, but further optimization is required; low yields (ca. 10–20%) of the desired products were obtained.
- ²⁷ Diastereomeric ratios observed in crude reaction mixtures were identical with those obtained upon isolation. In some cases the minor diastereomer could be separated by careful chromatography. See the Supporting Information for complete details.
- ²⁸ Preliminary efforts to employ a N1 Boc-protected substrate resulted in the formation of a 1:1 mixture of diastereomers. Attempts to cyclize substrates bearing N1 Piv or Ac groups have thus far been unsuccessful.
- ²⁹ Alkene insertion into late M-H bonds is usually much faster than alkene insertion into late M-C bonds. See: (a) Brookhart, M.; Hauptman, E.; Lincoln, D. M. *J. Am. Chem. Soc.* **1992**, *114*, 10394–10401. (b) Siegbahn, P. E. M.; Stromberg, S.; Zetterberg, K. *Organometallics* **1996**, *15*, 5542–5550.
- ³⁰ The formation of unsaturated five-membered heterocycles analogous to **III-69** and **III-70** is generally not observed in *N*-aryl-2-benzylpyrrolidine-forming reactions. Instead, the generation of regioisomeric *N*-aryl-2-methyl-3-arylpyrrolidine side products, which result

from reversible β -hydride elimination/reinsertion processes, is observed. These side products are usually formed in ca. 10% yield, whereas the combined yields of **III-69** and **III-70** is usually ca. 20-30%. For further discussion, see refs 8a and 8j.

³¹ Yamashita, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5344–5345.

³² These were not optimal conditions for the Boc cyclization and we optimized this reaction; however, we wanted to ensure all reaction conditions were the same in order to achieve a fair comparison in this investigation.

³³ A portion of this work has not been reported yet and is currently in preparation. Nakhla, J. S.; Schultz, D.M.; Wolfe, J. P. *Manuscript in Preparation*.

³⁴ The minor diastereomer is observed in minor amounts in the cyclization to afford **III-106**, but the diastereoselectivity is still >20:1.

³⁵ Cochran, B. M.; Michael, F. E. *Org. Lett.* **2008**, *10*, 329–332.

³⁶ This analysis is consistent with our own analysis. See reference 1.

³⁷ (a) Viso, A.; Fernandez de la Pradilla, R.; Flores, A.; Garcia, A.; Tortosa, M.; Lopez-Rodriguez, M. L. *J. Org. Chem.* **2006**, *71*, 1442–1448. (b) (a) Viso, A.; Fernandez de la Pradilla, R.; Lopez-Rodriguez, M. L.; Garcia, A.; Tortosa, M.; *SynLett* **2002**, 755–758.

³⁸ Lucet, D.; LeGall, T.; Mioskowski, C; *Angew. Chem. Int. Ed.* **1998**, *37*, 2580–2627.

³⁹ Felder, E.; Maffei, S.; Pietra, S.; Pitre, D. *Helv. Chim. Acta.* **1960**, *43*, 888–896.

⁴⁰ Morley, R. M.; Tse, H.-W.; Feng, B.; Miller, J. C.; Monaghan, D. T.; Jane, D. E. *J. Med. Chem.* **2005**, *48*, 2627–2637.

⁴¹ (a) Chuburu, F.; Tripier, R.; L Baccon, M.; Handel, H. *Eur. J. Org. Chem.* **2003**, 1050–1055. (b) Santes, V.; Gomez, E.; Zarate, V.; Santillan, R.; Farfan, N.; Rojas-Lima, S. *Tetrahedron: Asymmetry* **2001**, *12*, 241–247.

⁴² Mercer, G. J.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 1591–1594.

⁴³ The α -substituted allylic amines were synthesized either via the Overman rearrangement or using the Ellman reagent. For more details, see: (a) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901–2910. (b) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883–8904.

⁴⁴ The minor diastereomer in this reaction was isolated separately in combination with a 5-10% minor unidentified impurity.

⁴⁵ Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 3669–3679. Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828–1839.

⁴⁶ Anderson, W. K.; Lai, G. *Synthesis* **1995**, *10*, 1287–1290.

⁴⁷ This side product was isolated and characterized by ¹H, ¹H-COSY.

⁴⁸ Lu, Z.; Twieg, R. J. *Tetrahedron Lett.* 2005, *46*, 2997–3001.

⁴⁹ Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Synthesis* **2005**, 496–499.

Part Two

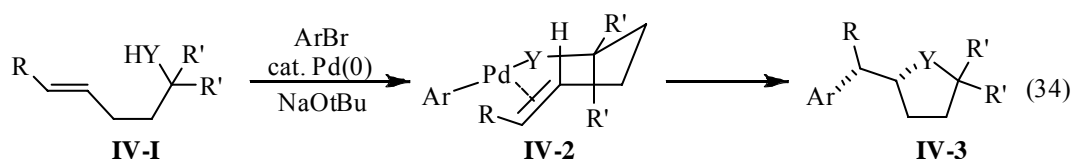
Intramolecular Pd-Catalyzed Carboetherification and Carboamination Reactions for the Synthesis of Tetrahydrofurans and Pyrrolidines

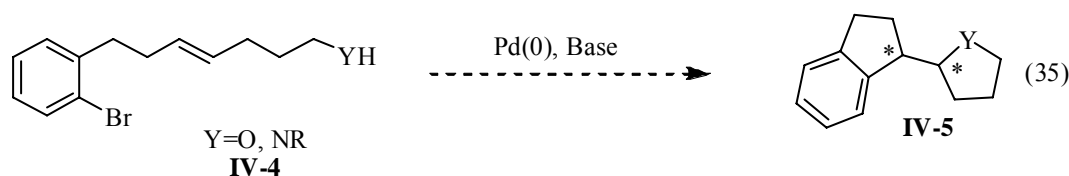
Chapter IV

Intramolecular Pd-Catalyzed Carboetherification and Carboamination Reactions

Introduction¹

For the past several years, our research group has explored the synthesis of tetrahydrofurans and pyrrolidines via Pd-catalyzed carboetherification and carboamination reactions of γ -unsaturated alcohols and amines with aryl and alkenyl halides (eq 34).² We felt that an interesting extension of this chemistry would involve alcohol and amine substrates bearing tethered aryl bromides (eq 35). We reasoned that this transformation could potentially be employed for the stereoselective construction of heterocycles bearing attached carbocyclic rings (**IV-5**), and would lead to the formation of two bonds, two stereocenters, and two rings in a single step (eq 35).³

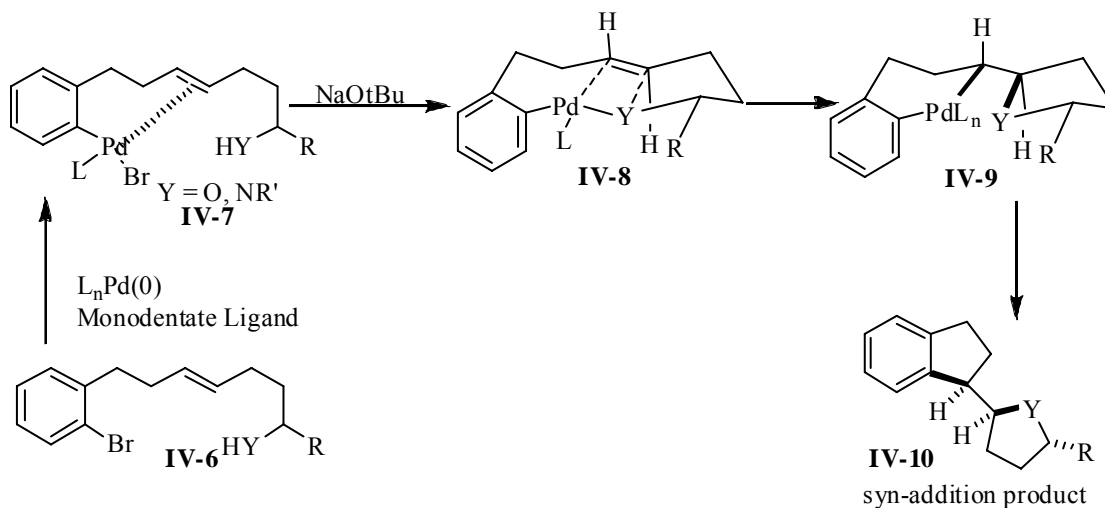




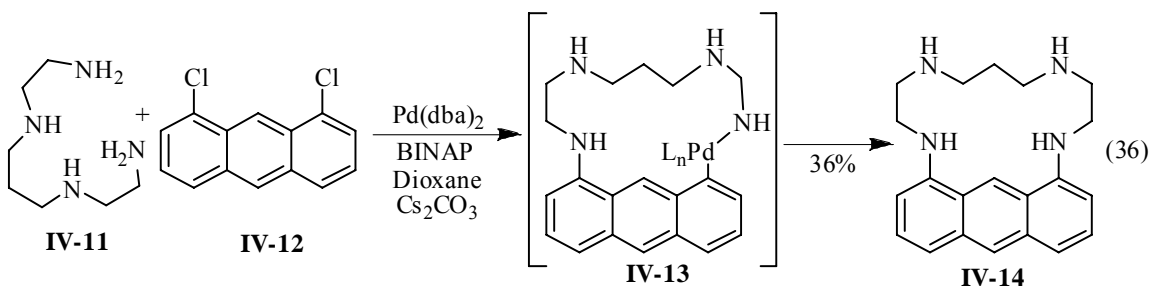
While the transformation in eq 35 is conceptually simple, there are several challenges associated with its execution. Transformations involving the intermolecular carboetherification reactions of internal olefins are currently limited to substrates bearing tertiary alcohol nucleophiles. Intermolecular carboamination reactions of *N*-aryl γ -amino internal olefins provided complex mixtures of products when acyclic internal alkenes were employed as substrates.⁴ In addition, the intramolecular reactions,⁵ if mechanistically analogous to the intermolecular reactions (eq 34), would involve a syn-alkene insertion of an 11-membered palladacyclic intermediate.

As shown in Scheme 37, oxidative addition of **IV-6** to Pd(0) followed by deprotonation and Pd–heteroatom bond formation affords **IV-8**. Syn-oxy- or amino-palladation followed by reductive elimination could then afford a product resulting from syn-addition of the oxygen and or nitrogen across the olefin (**IV-10**).

Scheme 37. Intramolecular Syn-Oxy- or Amino-palladation Mechanism

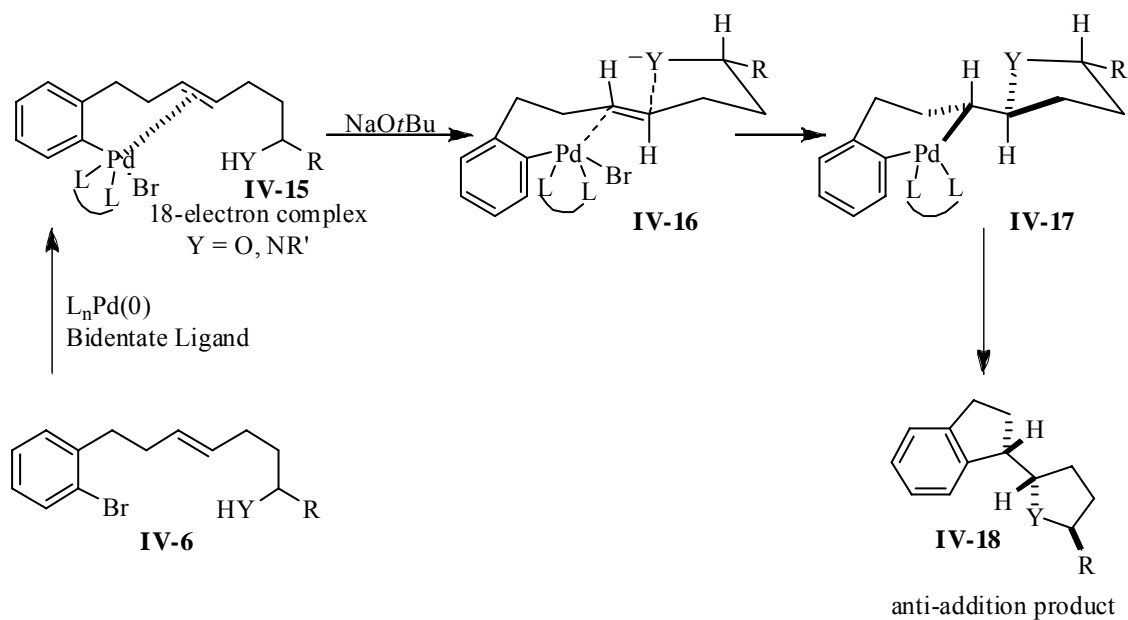


As shown in eq 36, only one previous report has described transformations that presumably involve macrocyclic palladacycles⁶ bearing both Pd–C and Pd–heteroatom bonds,⁷ and transannular syn-alkene insertions of macrocyclic palladacycles bearing internal olefins are unknown.



Product formation could also potentially occur through other mechanistic pathways that have not been previously observed to predominate in carboamination/carboetherification processes involving alkenes and aryl bromides.⁸ For example, oxidative addition of **IV-6** to Pd(0) followed by a Wacker-type anti-oxy-palladation would provide **IV-17**, which could undergo reductive elimination to afford **IV-18**. Although a priori we could not predict which pathway would predominate, both pathways seemed potentially viable, and we felt it might be possible to influence the mechanistic and stereochemical course of the reactions by varying catalyst structure.^{9,10}

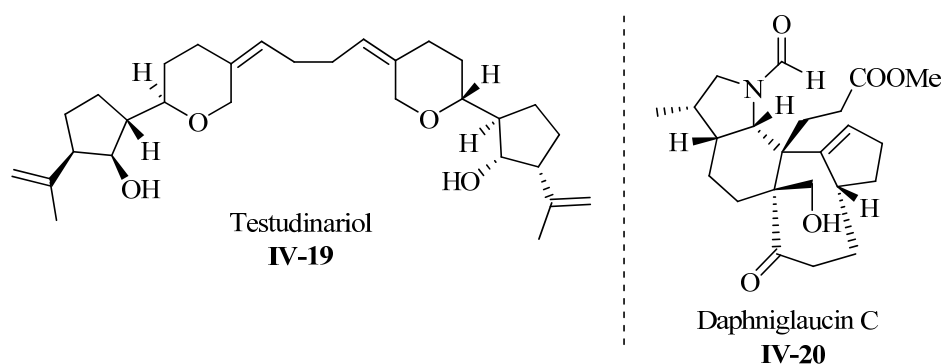
Scheme 38. Intramolecular Anti-Oxy- or Amino-palladation Mechanism



Background: Natural Products Containing Heterocycles Bearing Attached Carbocycles

Several interesting natural products contain heterocycles with attached carbocycles. The synthesis of these types of structures is challenging and common strategies employ methods by which the stereocenters are generated prior to ring closure.¹¹ To illustrate this point, several previously reported approaches to the synthesis of the molecule testudinariol are outlined below. Testudinariol (**IV-19**)¹² is an ichthyotoxic mollusk defensive allomone, and daphniglaucin C (**IV-20**)¹³ inhibits the polymerization of tubulin and is cytotoxic against lymphoma.

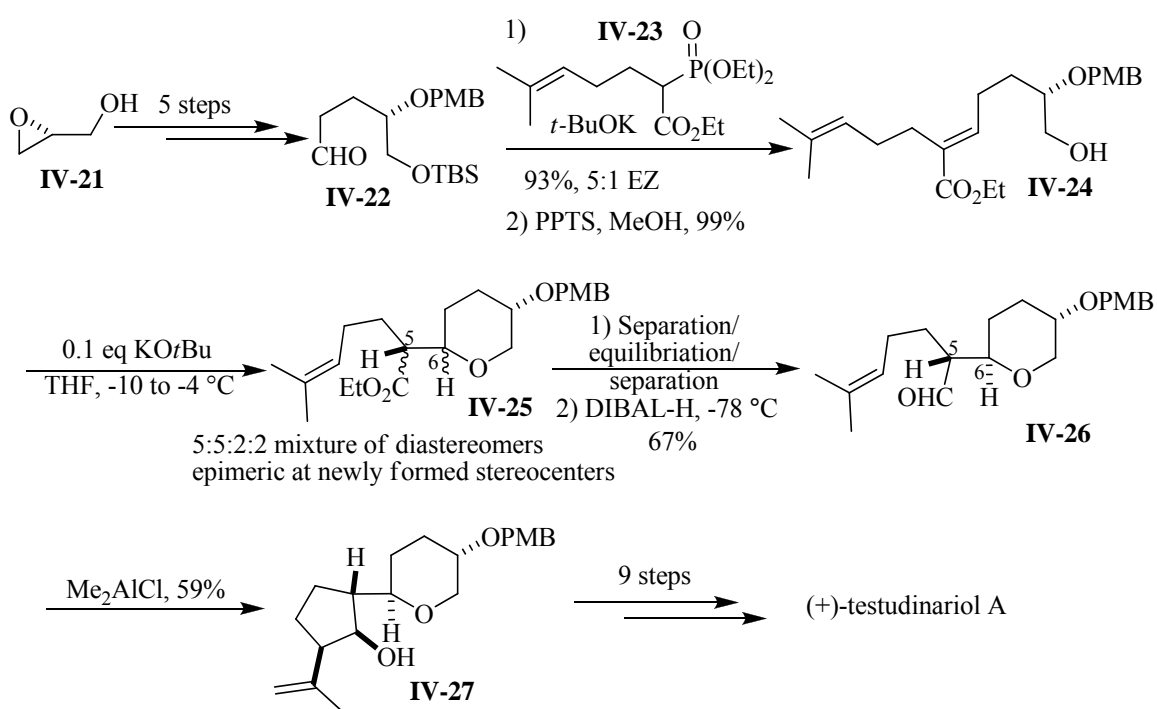
Figure 6. Natural Products containing Heterocycles with Attached Carbocycles



The synthesis of (+)-testudinariol has been undertaken by several groups. Mori¹⁴ reported the synthesis of (+)-testudinariol from (*R*)-glycidol which was converted to aldehyde **IV-22** in 5 steps. Horner Wadsworth Emmons olefination of **IV-22**, followed by deprotection provided trisubstituted olefin **IV-24**. The tetrahydropyran ring was formed using an intramolecular Michael addition under thermodynamic conditions to afford **IV-**

25 along with its three other diastereomers (5:5:2:2 ratio) epimeric at C5 and C6. Separation of the desired diastereomer was possible and the undesired isomers were resubjected to the equilibrating reaction conditions to afford an overall yield of 68% of the desired isomer. Reduction of the ester at C5 with DIBAL-H provides aldehyde **IV-26**, which undergoes a Lewis-acid mediated ene reaction¹⁵ in the presence of Me₂AlCl to form the carbocyclic ring in **IV-27**. The molecule is further elaborated to the natural product in several steps.

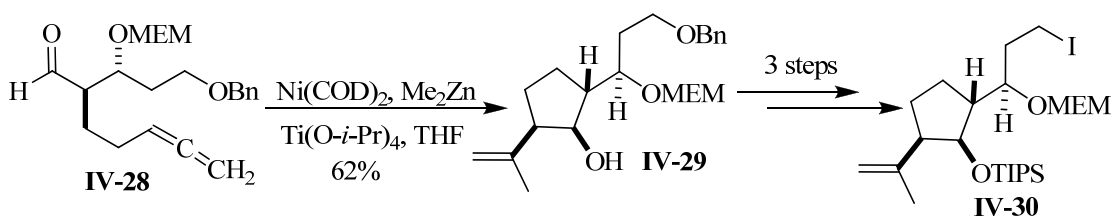
Scheme 39. Synthesis of (+)-Testudinariol A (**IV-20**) (Mori)



Montgomery prepared (+)-testudinariol using a Ni-catalyzed allenyl aldehyde cyclization to form the carbocyclic ring (**IV-29**) as shown below. The precursor **IV-28**

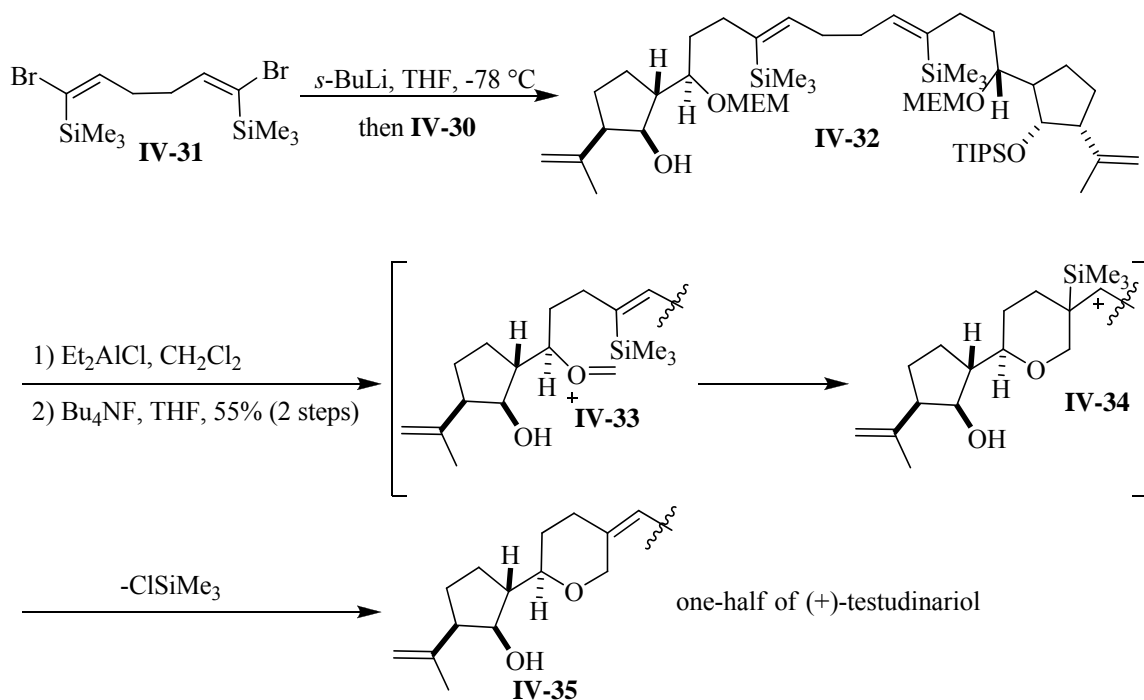
was prepared using an asymmetric aldol reaction. Deprotection, iodination and protection of the alcohol provided compound **IV-30**, which is used in the key coupling in Scheme 41.

Scheme 40. Synthesis of (+)-Testudinariol A Part I (Montgomery)



As shown in Scheme 41, bis(vinyl) silane is treated with *s*-BuLi to effect a metal-halogen exchange followed by treatment with alkyl iodide **IV-30** to afford the advanced intermediate **IV-32**. The final two steps involved a double oxycarbenium ion/vinyl silane cyclization (**IV-33** to **IV-35**) to form the tetrahydropyran ring followed by deprotection to afford the natural product.

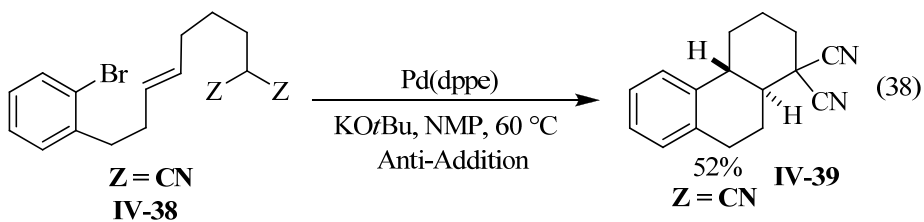
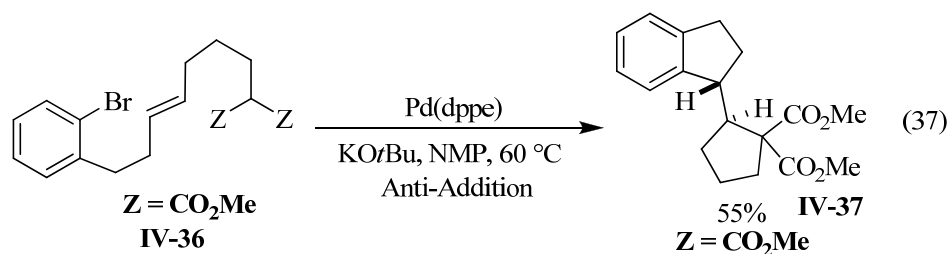
Scheme 41. Synthesis of (+)-Testudinariol A Part II (Montgomery)



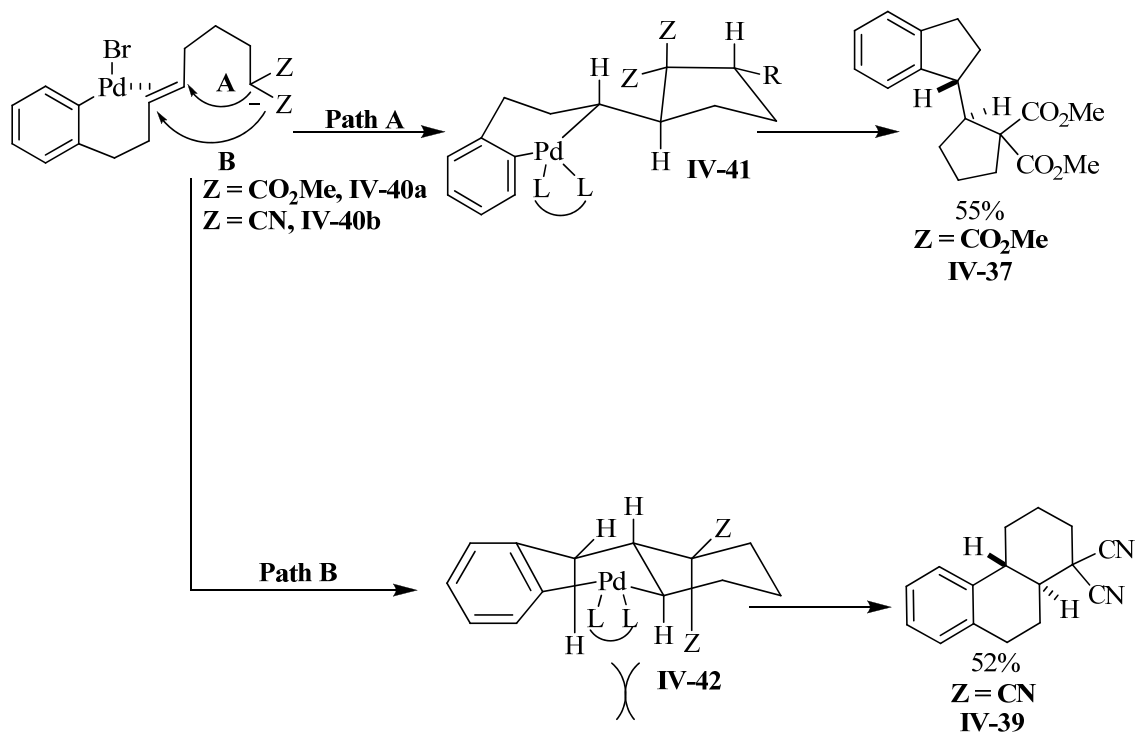
Background: Intramolecular Wacker-Type Carbopalladation Reactions

Balme has described elegant studies on related intramolecular reactions of alkenes with malonate nucleophiles (eq 37 and eq 38).¹⁶ These reactions proceed via oxidative addition of aryl bromides **IV-36** and **IV-38** to Pd(0) to generate **IV-40a** and **IV-40b** (Scheme 42). This intermediate then undergoes deprotonation followed by anti-addition of the malonate nucleophile and the organopalladium fragment across the alkene to provide **IV-41** or **IV-42**. Reductive elimination then generates the observed products **IV-37** or **IV-39**. The nature of the nucleophile is significant, and when Z = CO₂Et, five-membered ring formation occurs by attack through Path A. However, with Z = CN, six-membered ring formation is favored through Path B. The difference in regioselectivity

and its dependence on the nature of the nucleophile is not entirely clear, but the authors suggest that severe steric interactions between a bulkier nucleophile and the allylic hydrogens could account for preference to undergo the 6-endo mode of cyclization as shown in Path B of Scheme 42.



Scheme 42. Intramolecular Wacker-Type Carbopalladation Reactions



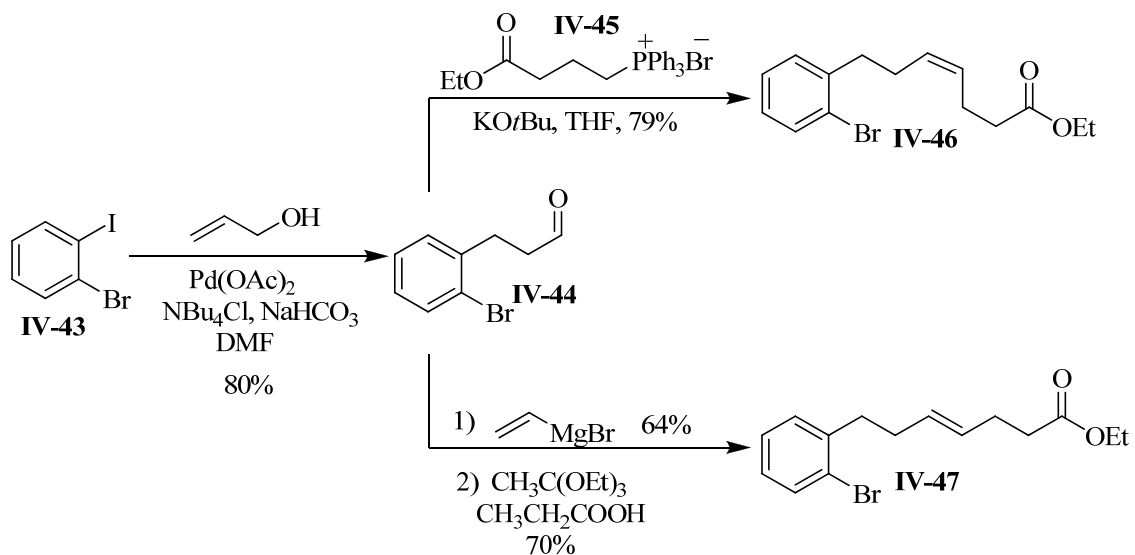
Development of Intramolecular Pd-Catalyzed Carboetherification and Carboamination Reactions

Our goals for the intramolecular Pd-catalyzed carboetherification and carboamination were to establish the feasibility of transforming unsaturated alcohols and amines bearing tethered aryl halides to 2-indan-1-yl tetrahydrofurans and pyrrolidines (eq 35). While we were concerned that the desired reaction would be outcompeted by various side reactions due to the more challenging internal olefin substrates, we felt that due to the intramolecular nature of the reaction as well as through proper catalyst optimization, we would be able to favor the desired transformation. Additionally, we hoped that through judicious choice of catalyst, we would be able to facilitate formation of either the syn-addition product or the anti-addition product.

Substrate Synthesis

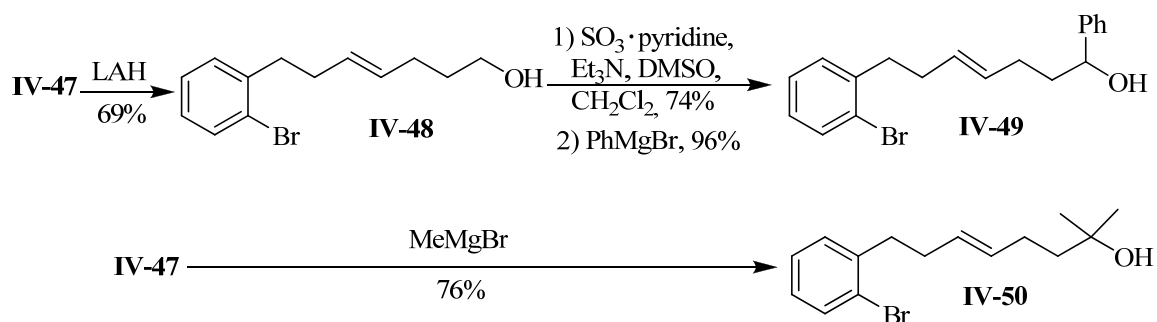
In our initial experiments we sought to examine the reactivity of several different types of substrates. For a complete study, we would need to selectively generate both *E*- and *Z*-alkene geometries (**IV-47** and **IV-46**) of substrates bearing both oxygen and nitrogen nucleophiles. In addition, we felt it would be essential to prepare substrates that were substituted α to the heteroatom in order to examine the diastereoselectivity of the reaction. Aldehyde **IV-44**, which served as common precursor to all substrates in this study was prepared via Heck reaction of allyl alcohol with 1-bromo-2-iodobenzene (**IV-43**) using Jeffrey conditions.¹⁷ This intermediate was converted to the *Z*-olefin (**IV-46**) by Wittig olefination using the ylide formed from deprotonation of 4-ethoxy-4-oxobutyl triphenylphosphonium bromide (**IV-45**). Alternatively, *E*-olefin **IV-47** was obtained by vinylmagnesium bromide addition into aldehyde **IV-44** followed by Johnson ortho ester Claisen rearrangement of the resulting allylic alcohol.^{16,18}

Scheme 43. Substrate Synthesis for Intramolecular Carboetherification and Carboamination Reactions-Synthesis of Key Intermediates **IV-46** and **IV-47**



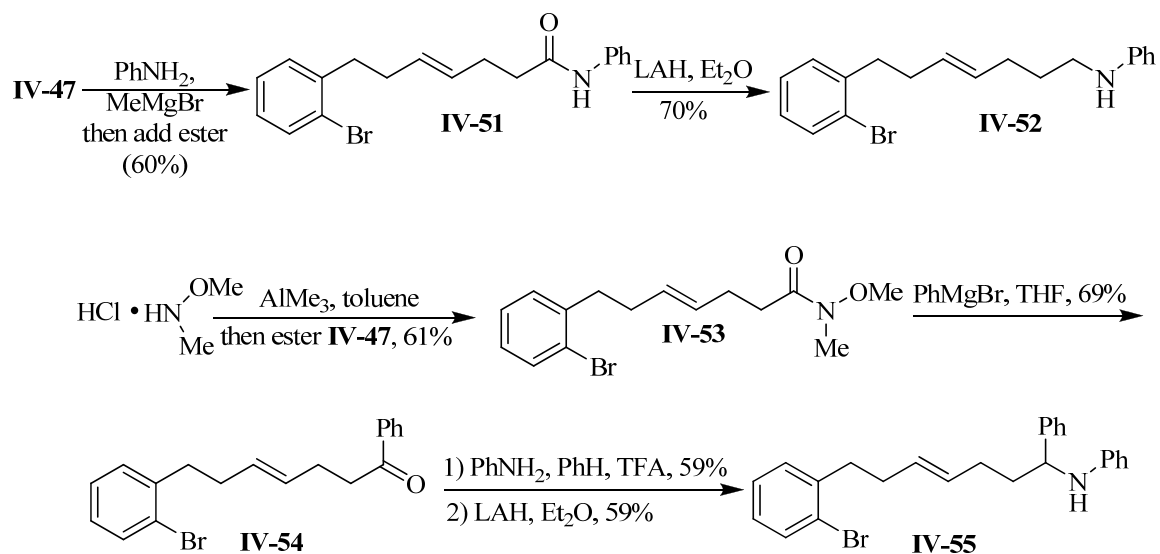
E and *Z* alkenes **IV-46** and **IV-47** were then transformed through functional group interconversions to the substrates needed for the study. Lithium aluminum hydride reduction of **IV-47** provides primary alcohol **IV-48**. Oxidation followed by addition of phenylmagnesium bromide provides the secondary alcohol **IV-49**. Methylmagnesium bromide addition into **IV-47** provides the tertiary alcohol **IV-50**.

Scheme 44. Substrate Synthesis of *E*-Hydroxy Alkenes-Synthesis of **IV-48**, **IV-49**, **IV-50**

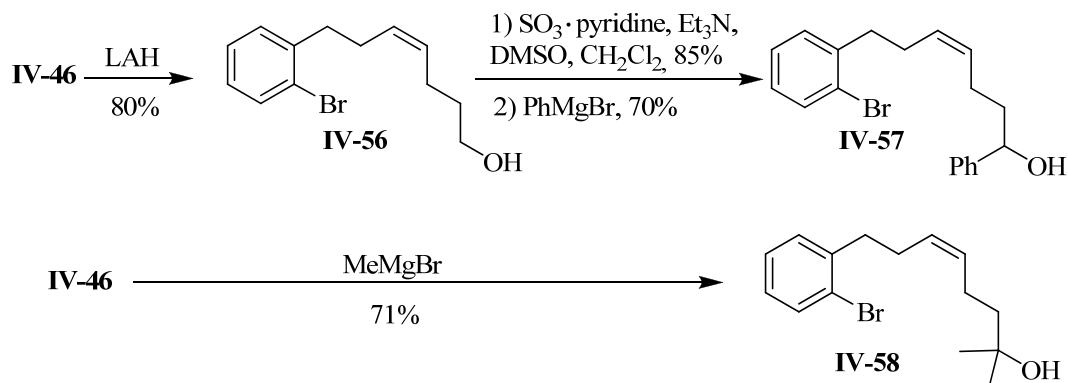


Deprotonation of aniline followed by addition of ester **IV-47** provided amide **IV-51**, which was reduced with lithium aluminum hydride to secondary amine **IV-52** (Scheme 45). The α -substituted secondary amine **IV-55** was formed via the reaction of methoxymethylamine hydrochloride with trimethylaluminum followed by addition of the ester **IV-47**. The Weinreb amide **IV-53** was then treated with phenylmagnesium bromide to afford the desired substrate **IV-54**. The alcohol and amine substrates bearing *Z*-alkenes were prepared from ester **IV-46** using an analogous series of transformations (Schemes 46 and 47).

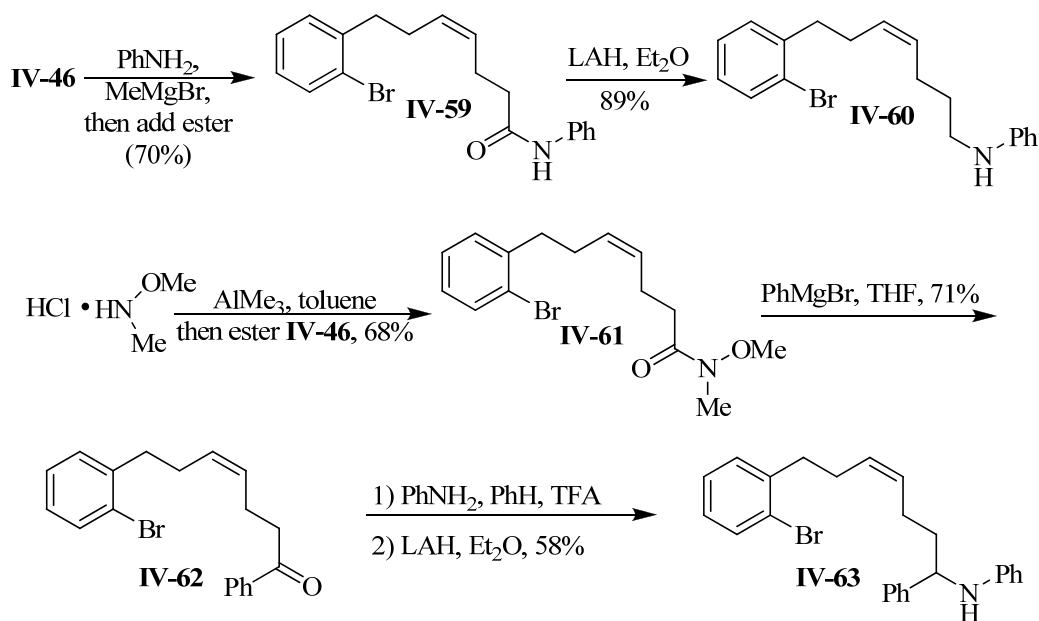
Scheme 45. Substrate Synthesis of *E*-Amino Alkenes-Synthesis of **IV-52**, **IV-55**



Scheme 46. Substrate Synthesis of *Z*-Hydroxy Alkenes-Synthesis of **IV-56**, **IV-57**, **IV-58**



Scheme 47. Substrate Synthesis of Z-Amino Alkenes-Synthesis of **IV-60**, **IV-63**

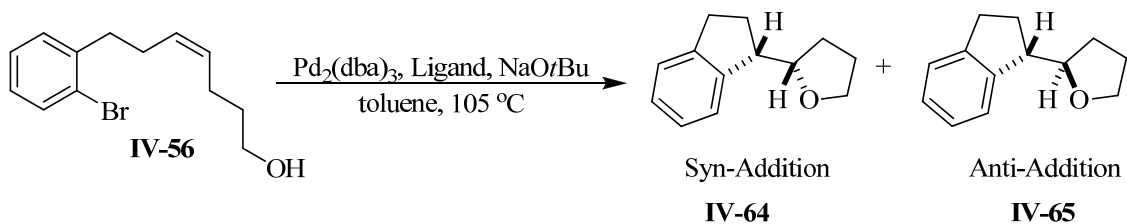


Intramolecular Carboetherification Reactions

In our initial experiments we elected to explore the intramolecular carboetherification of Z-alkene **IV-56** bearing a tethered primary alcohol group. We felt that the Z-alkene geometry of **IV-56** combined with the high nucleophilicity of the unhindered alkoxide (generated in situ upon reaction with NaOtBu) would help to facilitate formation of the putative 11-membered palladium-(aryl)(alkoxide) complex required for syn-alkoxypalladation as described above in Scheme 37. Our previous studies of Pd-catalyzed intermolecular carboetherification reactions demonstrated that the choice of phosphine ligand had a large impact on the chemical yield of the desired tetrahydrofuran products. Thus, our optimization studies focused on variation of this parameter while employing otherwise standard reaction conditions (toluene, NaOtBu, 105 °C).¹⁹

As shown in Table 16, we were gratified to find that Pd-catalyzed reactions of **IV-56** proceeded to generate the desired 2-(1-indanyl)tetrahydrofuran as a mixture of two diastereomers (**IV-64** and **IV-65**) in moderate to good yield with stereoselectivities dependent on catalyst structure. Use of a catalyst composed of Pd₂(dba)₃ and P(*o*-tol)₃ that provided optimal results in intermolecular carboetherification reactions of acyclic internal alkenes^{2b} afforded **IV-64** as the major diastereomer (entry 3), which derives from syn-addition of the arene and the alkoxide across the C=C double bond. The main side products observed in this reaction resulted from debromination of the starting material²⁰ or intramolecular Heck arylation of the alkene (Scheme 48). After some experimentation, a mixture of Pd₂(dba)₃ and P[(4-MeO)C₆H₄]₃ was found to provide product **IV-64** in 54% isolated yield with 8:1 diastereoselectivity (entry 1). Use of this catalyst system diminished the competing Heck arylation, although competing debromination of the substrate was still problematic.

A complete shift in the stereochemical outcome of this reaction was observed when (±)-BINAP was employed as the ligand (entry 8). Under these conditions, the (1*S**,2*R**)-diastereomer (**IV-65**) was formed as the major product. This substance derives from anti-addition of the arene and the alcohol across the double bond, and was obtained in 60% yield and 18:1 dr. Other chelating phosphine ligands with small bite angles such as DPPE and DPP-benzene also provided modest selectivity for the anti-addition product.

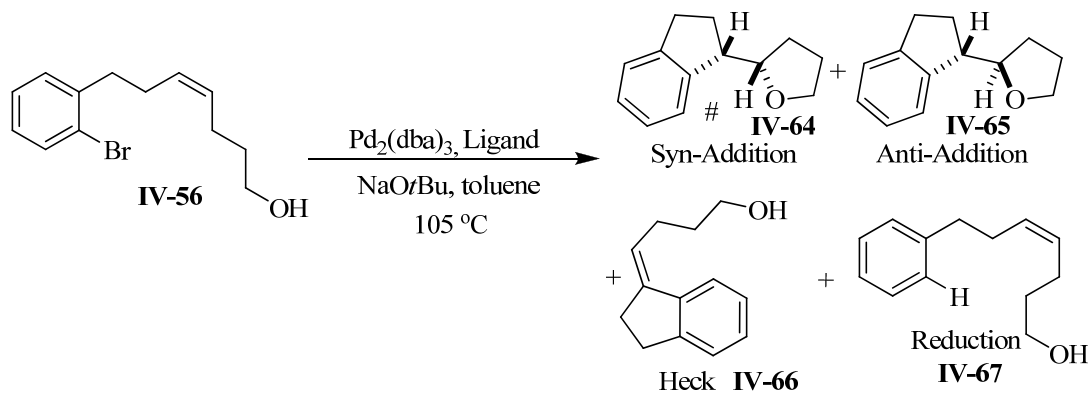
Table 16. Optimization of Carboetherification Reaction of **IV-56**^{a,b}

Entry	Ligand	Isolated yield	dr (<i>syn:anti</i>)
1	P[(<i>p</i>-MeO)C₆H₄]₃	54	8:1
2	PPh ₃	27	5:1
3	P(<i>o</i> -tol) ₃	35	2:1
4	PCy ₃	48	2:1
5	DPE-Phos	49	1:1
6	DPPE	46	1:2
7	DPP-Benzene	44	1:2
8	(±)-BINAP	60	1:18

^aConditions: 1.0 equiv of **IV-56**, 2.0 equiv of NaOtBu, 1 mol % Pd₂(dba)₃, 4 mol % ligand (monophosphines) or 2 mol % ligand (bisphosphines), toluene (0.1 M), 105 °C, 3-8 h.

^bDiastereoselectivities were determined by GC and/or ¹H NMR analysis of crude reaction mixtures.

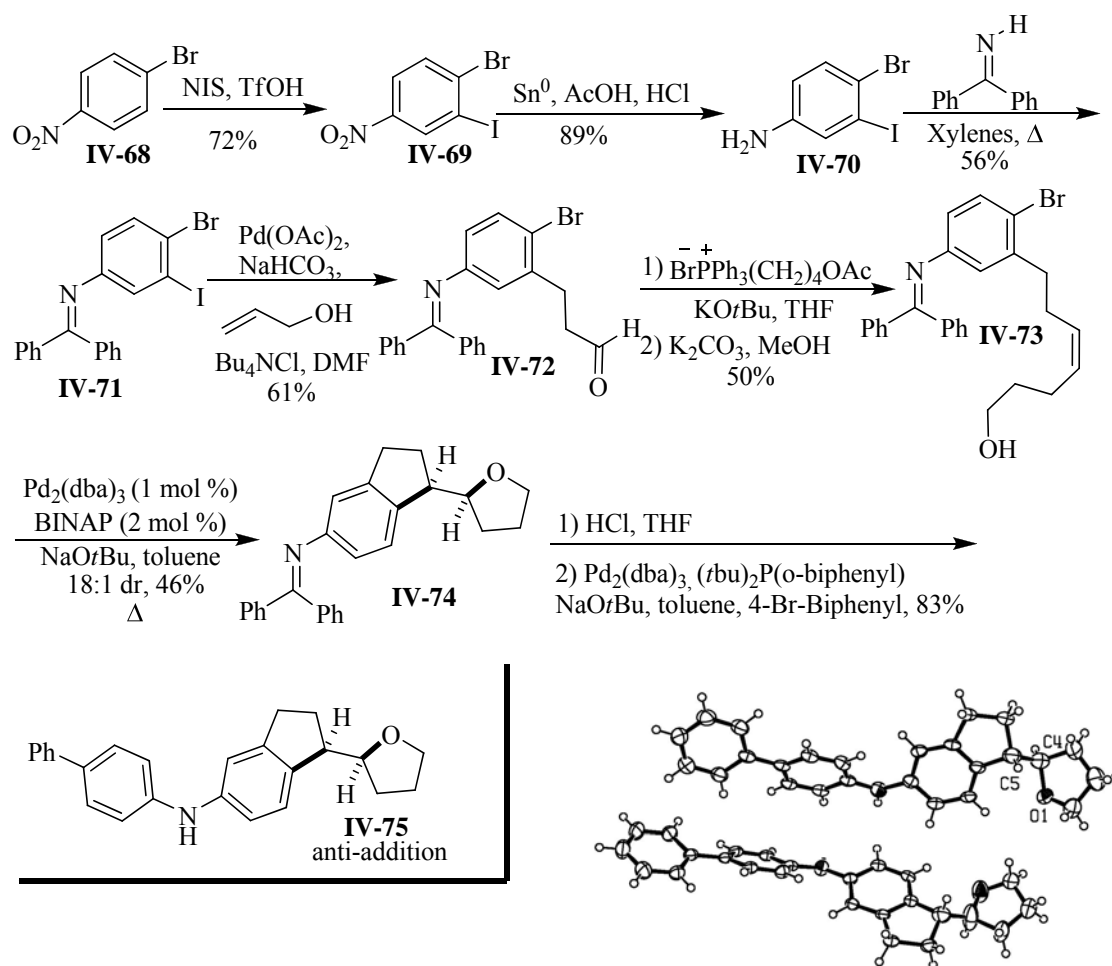
Scheme 48. Products of Pd-Catalyzed Carboetherification of **IV-56**



The connectivity of **IV-64** and **IV-65** was determined through 2D COSY and HSQC NMR experiments. The stereochemistry of **IV-64** and **IV-65** was established by X-ray crystallographic analysis of related derivative **IV-75**. This product was prepared as shown in Scheme 49. Iodination of 4-bromonitrobenzene (**IV-68**) provides iodo arene **IV-69**. The nitro functionality in **IV-69** was reduced with tin granules in acetic acid to provide **IV-70**. Transamination of **IV-70** with benzophenone imine afforded protected amine **IV-71**. Heck reaction of **IV-71** under Jeffrey phosphine-free conditions provided aldehyde **IV-72** which was olefinated with the ylide generated from (4-acetoxybutyl)triphenylphosphonium bromide and KOtBu . Deprotection of the acylated alcohol provided alcohol **IV-73**. Intramolecular carboetherification of **IV-73** using catalytic $\text{Pd}_2(\text{dba})_3/\text{BINAP}$ afforded **IV-74** in modest yield with good diastereoselectivity. However, compound **IV-74** was not found to be a solid. Cleavage of the benzophenone imine functionality followed by *N*-arylation of the primary amine with 4-bromobiphenyl afforded the solid biphenyl derivative **IV-75**. X-ray crystal structure analysis of this

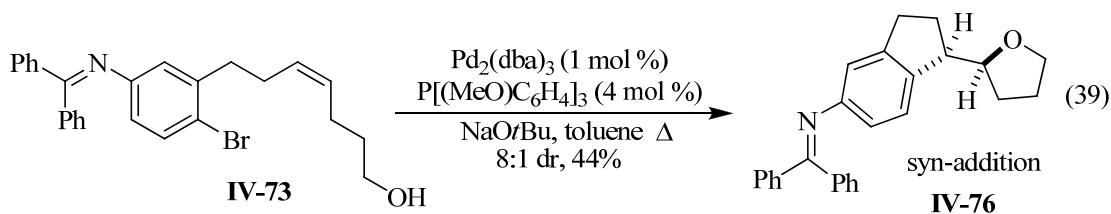
product (X-ray showed both enantiomers in the unit cell) revealed the cyclization occurred with anti-addition across the *Z*-alkene.

Scheme 49. Proof of Stereochemistry-Preparation and X-ray Structure of **IV-75**

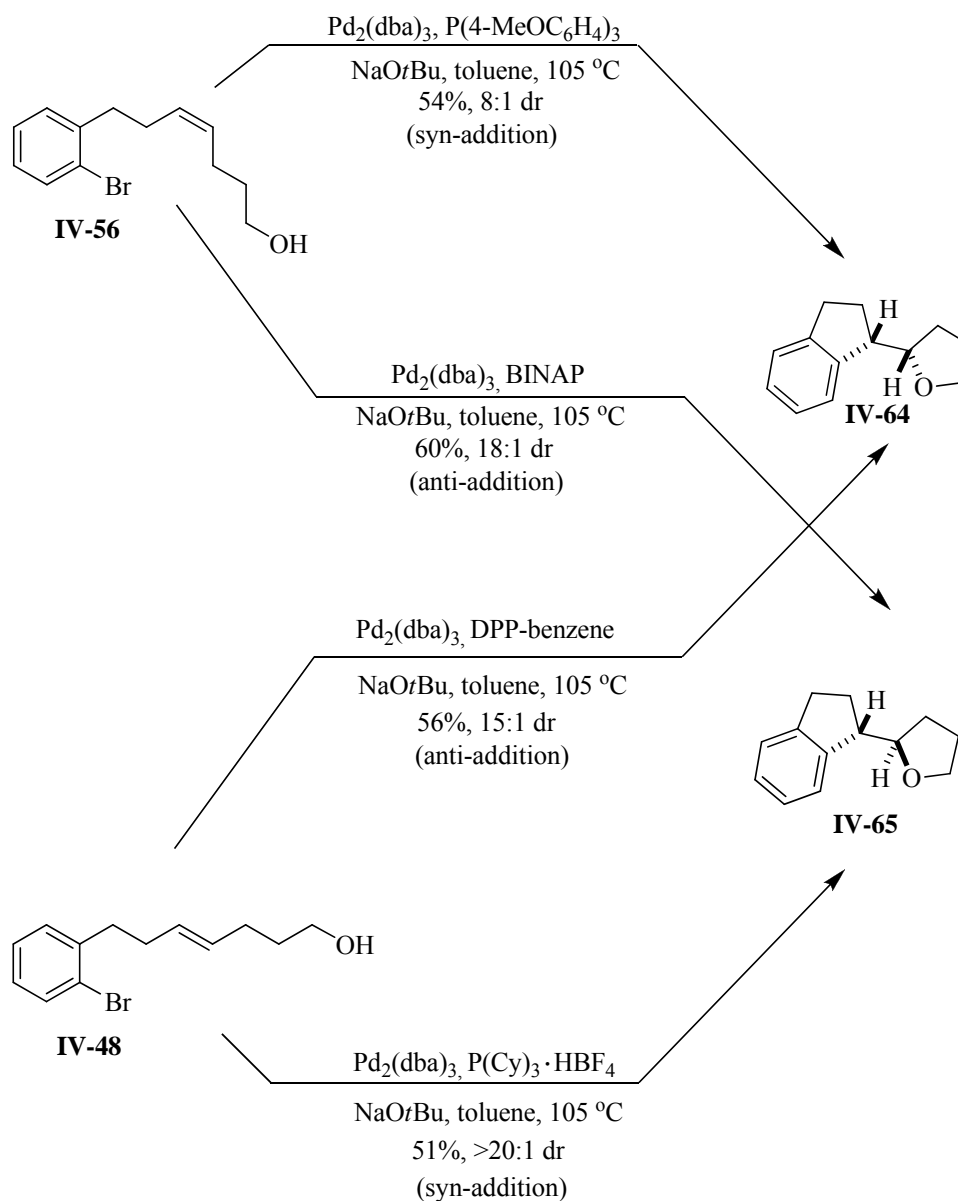


As expected, use of $\text{P}[(p\text{-MeO})\text{C}_6\text{H}_4]_3$ as ligand provided the opposite diastereomer (**IV-76**) in 44% yield and 8:1 dr (eq 39). Connectivity of **IV-76** was confirmed by 2D COSY and HSQC NMR experiments. With optimized reaction

conditions in hand, we examined the intramolecular carboetherification of several different alcohol substrates with varying alkene geometries and varied degrees of alcohol substitution. As shown in Scheme 50, the transformations of substrates bearing primary alcohols were found to be stereospecific, and either diastereomer could be selectively obtained from either the *E*- or *Z*-alkene starting material (**IV-56** or **IV-48**) with the appropriate choice of catalyst. For example, the (1*S**,2*R**)-2-indan-1-yl tetrahydrofuran **IV-65** was generated in 51% yield and >20:1 dr via the Pd/PCy₃-catalyzed syn-addition reaction of *E*-alkene substrate **IV-48**²¹ and was obtained in 60% yield and 18:1 dr via the Pd/(±)-BINAP-catalyzed anti-addition of *Z*-alkene substrate **IV-56**. Similarly, the (1*S**,2*S**)-isomer **IV-64** was produced in 56% yield (15:1 dr) from **IV-48** with DPP-benzene as ligand, and 54% yield (8:1 dr) from **IV-56** with the ligand P[(*p*-MeO)C₆H₄]₃.



Scheme 50. Intramolecular Carboetherification of **IV-56** and **IV-48**^{a, b}



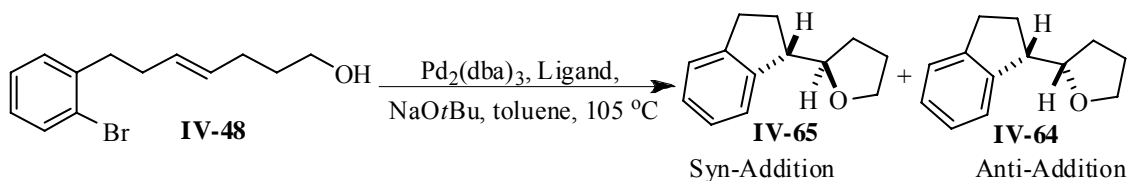
^aConditions: 1.0 equiv of **IV-56** or **IV-48**, 2.0 equiv of NaOtBu , 1 mol % $\text{Pd}_2(\text{dba})_3$, 4 mol % ligand (monophosphines) or 2 mol % ligand (bisphosphines), toluene (0.1 M), $105\text{ }^\circ\text{C}$, 3-8 h.

^bDiastereoselectivities were determined by GC and/or ^1H NMR analysis of crude reaction mixtures.

Additional data on ligand effects in the carboetherification of **IV-48** are shown below (Table 17). While the cyclization of **IV-48** proceeded under optimal conditions to

provide the anti-diastereomer with DPP-benzene, use of BINAP as ligand also selectively afforded the anti-diastereomer **IV-64** but with 3:1 dr and in 35% yield.

Table 17. Carboetherification Ligand Screen of **IV-48**^{a,b}



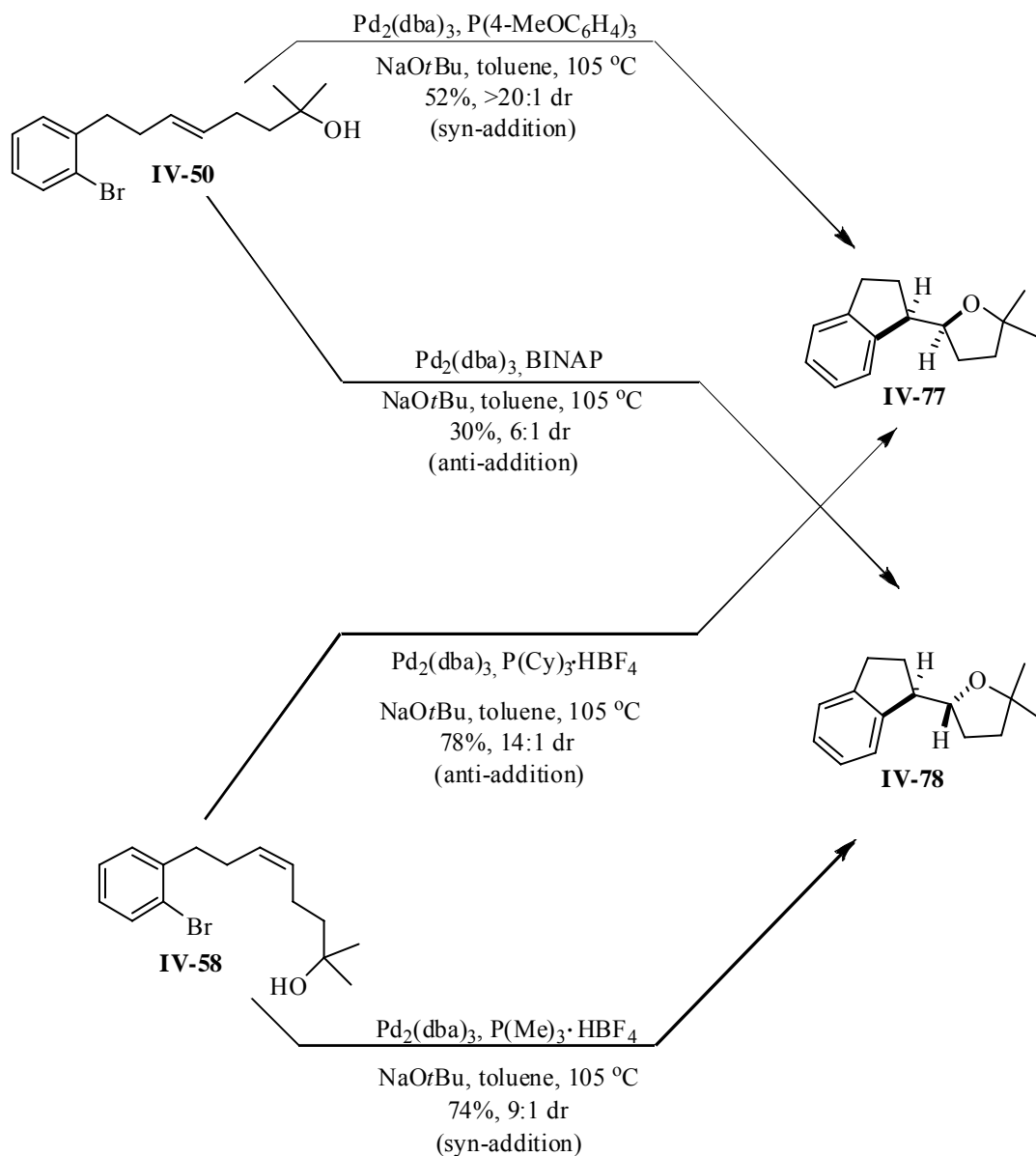
Entry	Ligand	Isolated yield	dr (<i>syn:anti</i>)
1	PCy₃	51	>20:1
2	P[(<i>p</i> -MeO)C ₆ H ₄] ₃	33	>20:1
3	(±)-BINAP	35	1:3
4	DPP-Benzene	56	1:15

^aConditions: 1.0 equiv of **IV-48**, 2.0 equiv of NaOtBu, 1 mol % Pd₂(dba)₃, 4 mol % ligand (monophosphines) or 2 mol % ligand (bisphosphines), toluene (0.1 M), 105 °C, 3-8 h.
^bDiastereoselectivities were determined by GC and/or ¹H NMR analysis of crude reaction mixtures.

Substrates **IV-50** and **IV-58** bearing tethered tertiary alcohols were also selectively converted to products of either syn- or anti-addition depending on catalyst structure (Scheme 51). However, in contrast to reactions of *Z*-alkene primary alcohol **IV-56**, which afforded syn-addition product **IV-64** with most catalyst systems, transformations of the analogous tertiary alcohol bearing a *Z*-alkene (**IV-58**) gave anti-addition product **IV-77** under most conditions examined (Table 18). After some experimentation, the Pd/PMe₃·HBF₄-catalyzed reaction of **IV-58** was found to provide **IV-78**,²¹ the product of syn-addition across the *Z*-alkene, in 74% yield with 9:1 dr. Use of the ligand PCy₃·HBF₄ for the Pd-catalyzed cyclization of **IV-58** afforded anti-addition

product **IV-77** in 78% yield and 14:1 dr. Although both diastereomers **IV-77** and **IV-78** could be selectively obtained from either starting material (**IV-50** or **IV-58**), higher yields were obtained with the *Z*-alkene substrate **IV-58**.

Scheme 51. Intramolecular Carboetherification of **IV-50** and **IV-58**^{a,b}

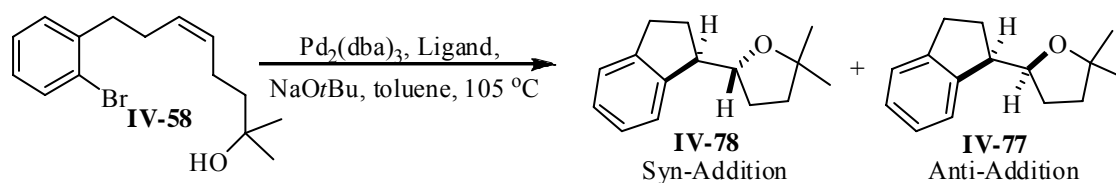


^aConditions: 1.0 equiv of **IV-50** or **IV-58**, 2.0 equiv of NaOtBu , 1 mol % $\text{Pd}_2(\text{dba})_3$, 4 mol % ligand (monophosphines) or 2 mol % ligand (bisphosphines), toluene (0.1 M), 105 °C, 3-8 h.

^bDiastereoselectivities were determined by GC and/or ^1H NMR analysis of crude reaction mixtures.

Additional data on ligand effects in the cyclization of *Z*-tertiary alcohol **IV-76** are provided below (Table 18). As noted above, all ligands except $\text{PMe}_3 \cdot \text{HBF}_4$ selectively provided the anti-addition product. The $\text{Pd}_2(\text{dba})_3/\text{BINAP}$ catalyst system also provided the anti-addition product as the major diastereomer, albeit in low yield (24%). Additional data on ligand effects in the cyclization of *E*-tertiary alcohol **IV-50** are also provided below in Table 19.

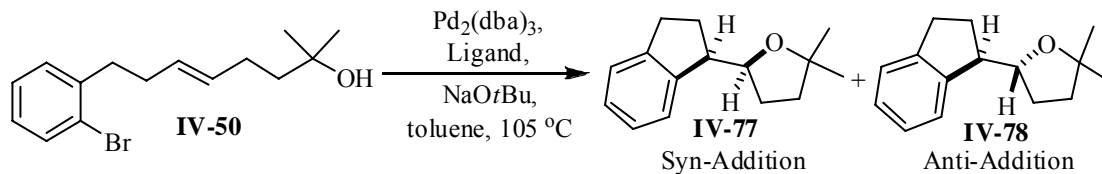
Table 18. Carboetherification Ligand Screen of **IV-58**^{a,b}



Entry	Ligand	dr (<i>syn:anti</i>)	Isolated yield
1	(±)-BINAP	1:20	24
2	$\text{P}(\text{Cy})_3 \cdot \text{HBF}_4$	1:14	78
3	$\text{P}[(p\text{-MeO})\text{C}_6\text{H}_4]_3$	1:2.44	61
4	$\text{P}(2\text{-fur})_3$	1:2.3	--
5	$\text{P}[(2,4,6\text{-MeO})\text{C}_6\text{H}_4]_3$	1:2.4	--
6	$\text{PEt}_3 \cdot \text{HBF}_4$	1:1	--
7	$\text{PMe}_3 \cdot \text{HBF}_4$	9:1	74

^aConditions: 1.0 equiv of **IV-58**, 2.0 equiv of NaOtBu , 1 mol % $\text{Pd}_2(\text{dba})_3$, 4 mol % ligand (monophosphines) or 2 mol % ligand (bisphosphines), toluene (0.1 M), $105\text{ }^\circ\text{C}$, 3-8 h.

^bDiastereoselectivities were determined by GC and/or ^1H NMR analysis of crude reaction mixtures.

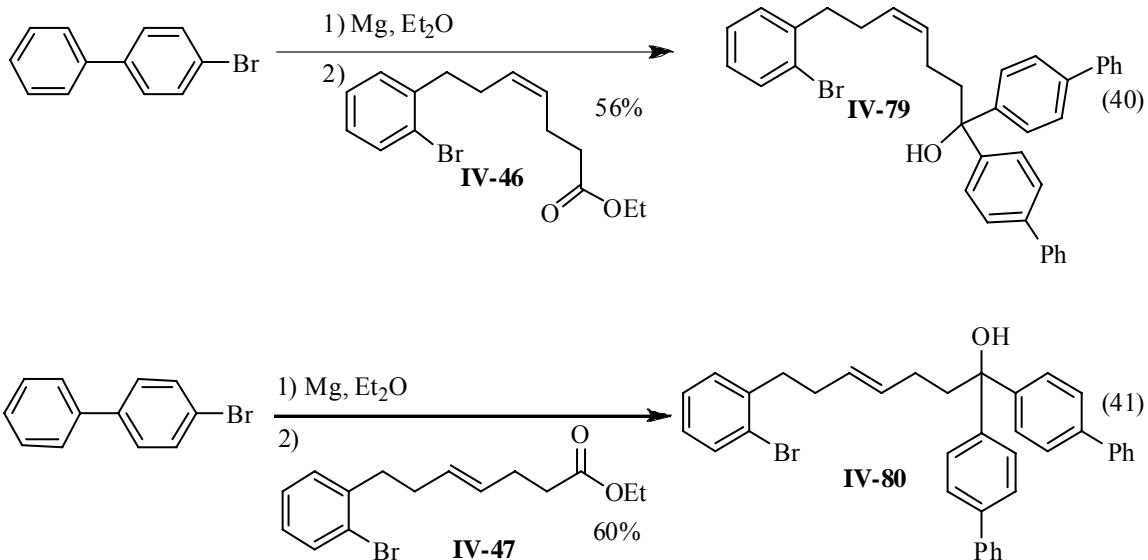
Table 19. Carboetherification Ligand Screen of **IV-50**^{a,b}

Entry	Ligand	dr (<i>syn:anti</i>)	Isolated yield
1	(±)-BINAP	1:6	30
2	DPP-Benzene	1:5	--
3	$\text{P}[(2,4,6\text{-MeO})\text{C}_6\text{H}_4]_3$	2:1	61
4	$\text{P}(\text{Cy})_3\cdot\text{HBF}_4$	5:1	66
5	$\text{P}[(p\text{-MeO})\text{C}_6\text{H}_4]_3$	>20:1	52

^aConditions: 1.0 equiv of **IV-50**, 2.0 equiv of NaOtBu , 1 mol % $\text{Pd}_2(\text{dba})_3$, 4 mol % ligand (monophosphines) or 2 mol % ligand (bisphosphines), toluene (0.1 M), $105\text{ }^\circ\text{C}$, 3-8 h.

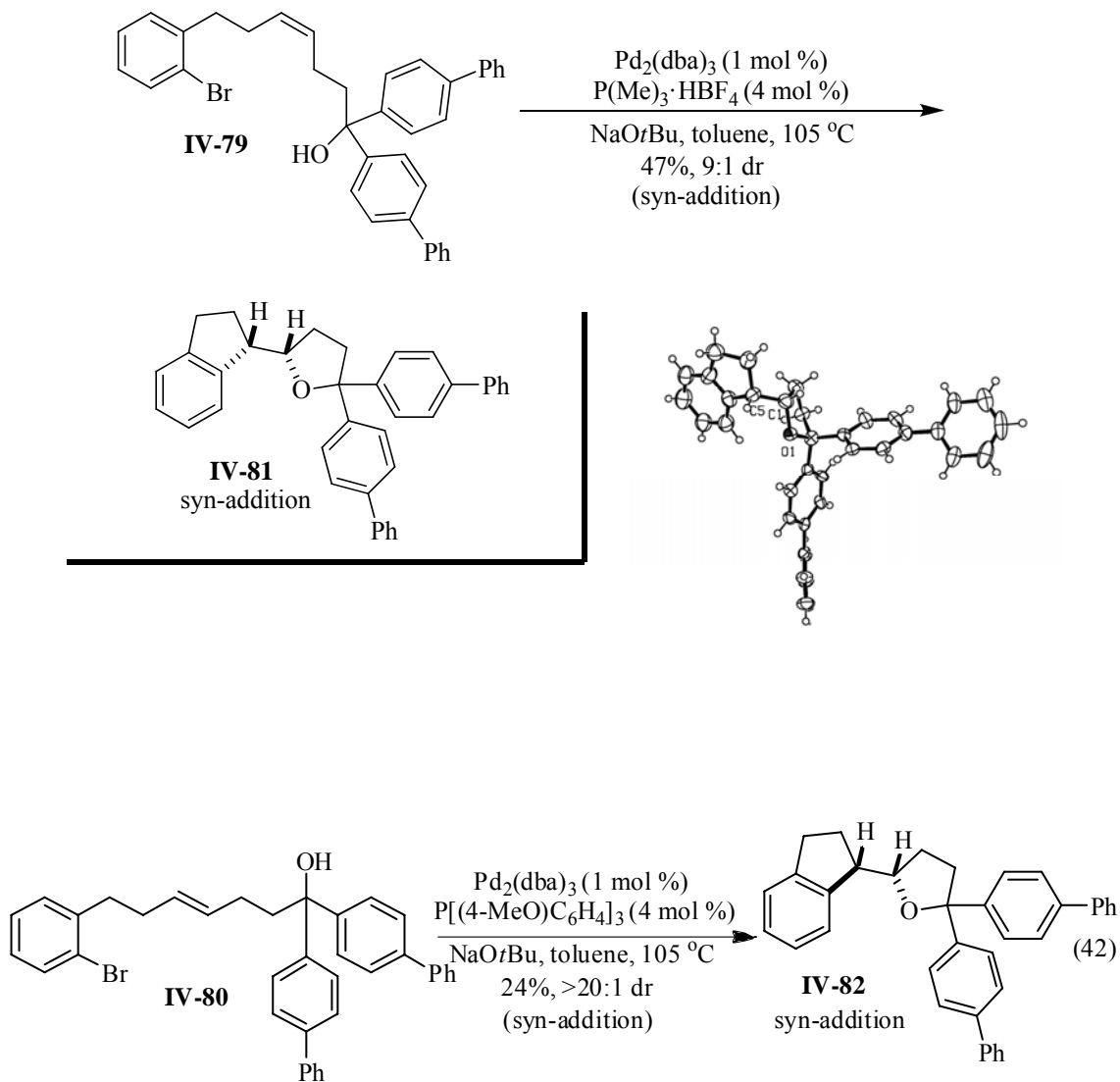
^bDiastereoselectivities were determined by GC and/or ^1H NMR analysis of crude reaction mixtures.

In order to definitively establish the stereochemistry of tetrahydrofuran products **IV-77** and **IV-78**, X-ray crystal structure analysis of the crystalline derivative (**IV-81**) shown in eq 52 was performed. The *E*- and *Z*-tertiary alcohol substrates were prepared via addition of *p*-biphenylmagnesium bromide to esters **IV-46** and **IV-47** as shown in eq 40 and 41.



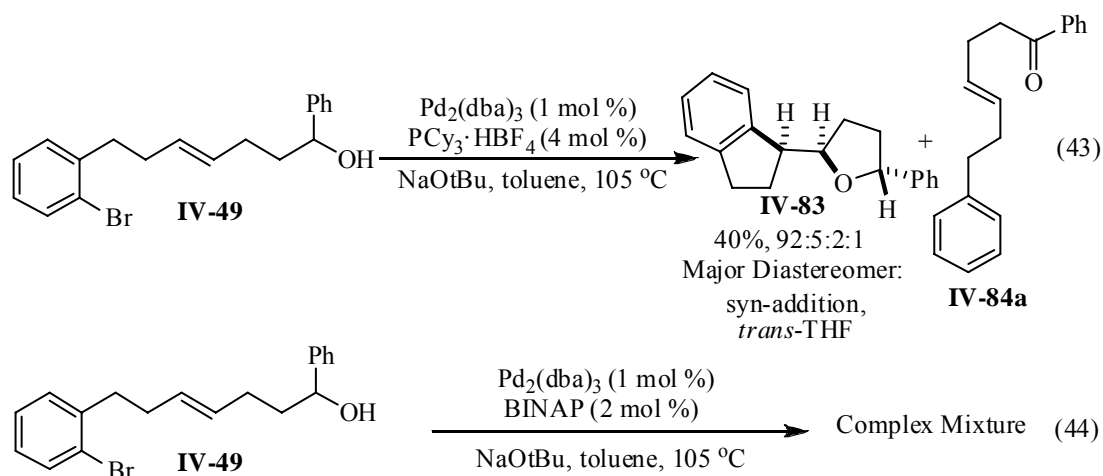
The reaction of tertiary alcohol **IV-79** to provide tetrahydrofuran **IV-81** proceeds with Pd/PMe₃·HBF₄ as the catalyst to provide the product resulting from syn-addition across the *Z*-olefin. Carboetherification of tertiary alcohol **IV-80** using P[(4-MeO)C₆H₄]₃ as the ligand provides the product of syn-addition across the *E*-olefin (**IV-82**). The connectivity of these molecules was further confirmed by 2D-NMR COSY and HSQC experiments.

Scheme 52. Proof of Stereochemistry-Preparation and X-ray Structure of **IV-81**

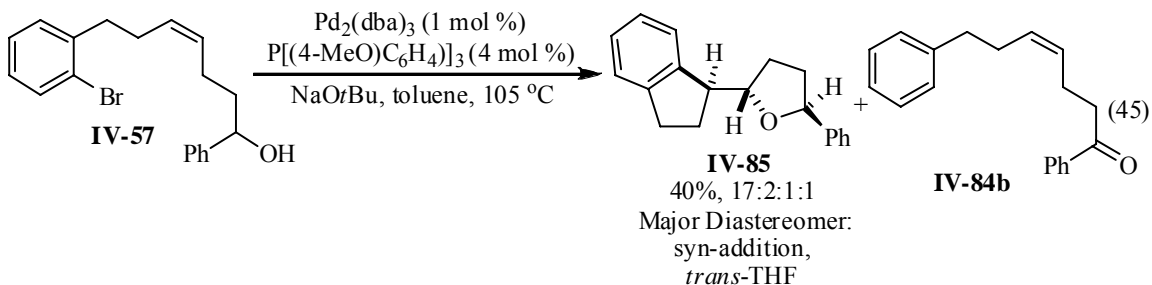


To examine the possibility of stereoselectively generating products with three stereocenters, the secondary alcohol **IV-49** bearing an *E*-alkene was prepared and subjected to the carboetherification reaction conditions. The best results were obtained with a catalyst composed of $\text{Pd}_2(\text{dba})_3/\text{PCy}_3 \cdot \text{HBF}_4$, which provided a 40% isolated yield of **IV-83** with 92:5:2:1 selectivity favoring syn-addition across the alkene and *trans*-

stereochemistry around the tetrahydrofuran ring (eq 43). The modest yield can be attributed to the formation of large amounts of side products that derive from reduction of the aryl bromide with concomitant oxidation of the alcohol (eq 43). Use of (\pm)-BINAP for this transformation led to complex mixtures of products; only small amounts of the desired tetrahydrofuran derivatives were detected by ^1H NMR analysis of crude reaction mixtures (eq 44).



The cyclization of the corresponding *Z*-alkene **IV-57** proceeded in 40% yield with good selectivity (17:2:1:1 dr)²² for syn-addition/*trans*-THF formation (eq 45); the two most prevalent diastereomers both contained *trans*-tetrahydrofuran rings. As noted above, competing oxidation/reduction of the substrate was problematic in this system.



In contrast to the related Pd/BINAP-catalyzed reaction of the *E*-alkene substrate **IV-49**, treatment of **IV-57** with catalytic Pd₂(dba)₃/(\pm)-BINAP provided **IV-83** as the major diastereomer, which results from anti-addition with *trans*-THF formation, albeit in low yield (25%) (eq 46). High selectivity for anti-addition was observed (94:6), although *trans*/*cis*-selectivity was modest (ca. 2:1). The major side products in this transformation resulted from competing intramolecular Heck arylation of the starting material. A summary of the ligand effects for both the *E*- and *Z*-secondary alcohols is shown in Tables 20 and 21 below.

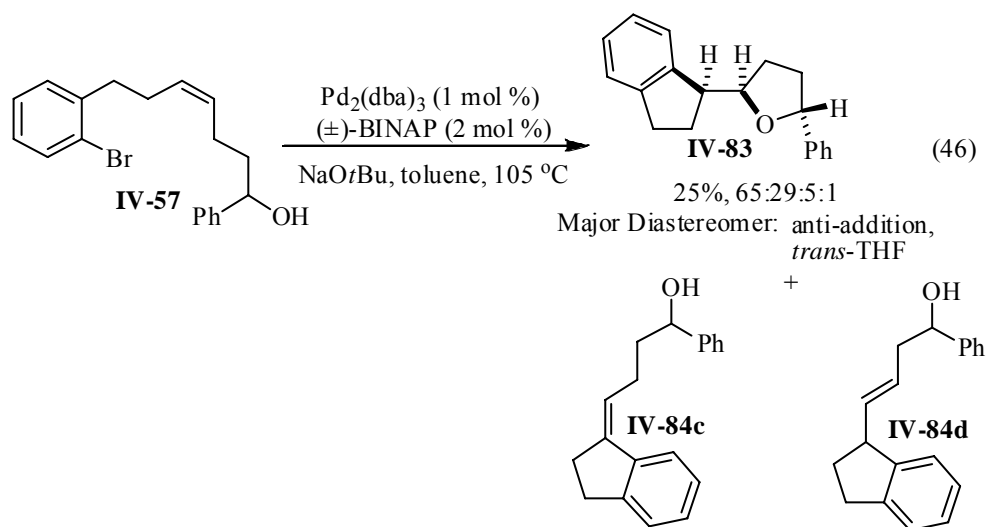
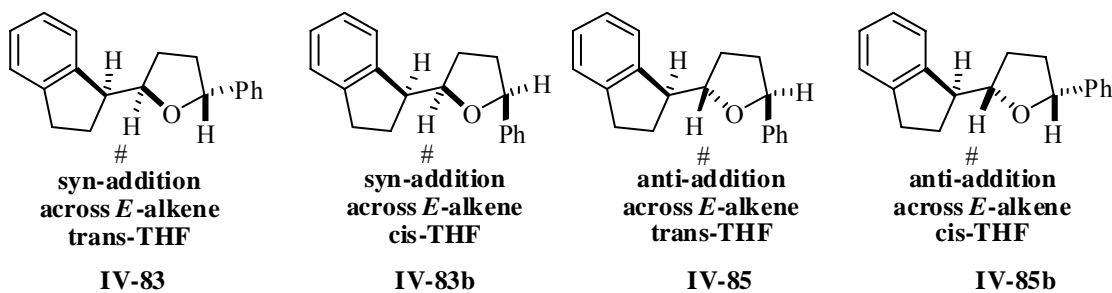
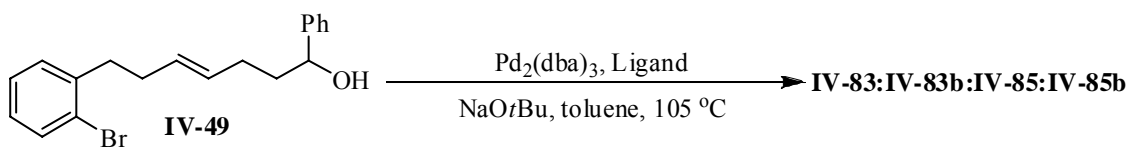
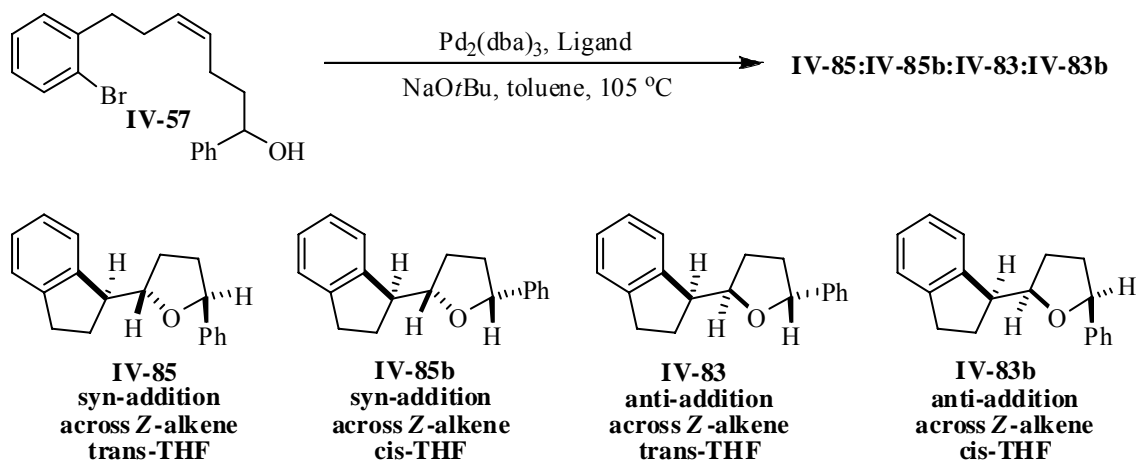


Table 20. Carboetherification Ligand Screen of **IV-49**^{a,b}



Ligand	Diastereomeric Ratio	Isolated Yield	Syn/Anti	Trans:Cis
PCy ₃	92: 5: 2: 1	40%	32:1	15:1
P[(4-MeO)C ₆ H ₄] ₃	75: 0: 25: 0	25%	4:1	4:0
BINAP	21: 28: 9: 42	---	1:1	2:1

^aConditions: 1.0 equiv of **IV-49**, 2.0 equiv of NaOtBu, 1 mol % Pd₂(dba)₃, 4 mol % ligand (monophosphines) or 2 mol % ligand (bisphosphines), toluene (0.1 M), 105 °C, 3-8 h.
^bDiastereoselectivities were determined by GC and/or ¹H NMR analysis of crude reaction mixtures.

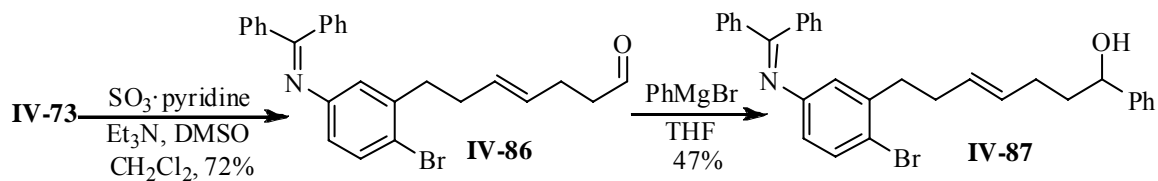
Table 21. Carboetherification Ligand Screen of **IV-57**^{a,b}

Ligand	Diastereomeric Ratio A: B: C: D	Isolated Yield	Syn/Anti	Trans:Cis
P[(4-MeO)C ₆ H ₄] ₃	75: 6: 12: 7	40%	4:1	7:1
PCy ₃	40: 8: 40: 12	23%	1:1	4:1
BINAP	5: 1: 65: 29	24%	1:33	3:1

^aConditions: 1.0 equiv of **IV-57**, 2.0 equiv of NaOtBu, 1 mol % Pd₂(dba)₃, 4 mol % ligand (monophosphines) or 2 mol % ligand (bisphosphines), toluene (0.1 M), 105 °C, 3-8 h.
^bDiastereoselectivities were determined by GC and/or ¹H NMR analysis of crude reaction mixtures.

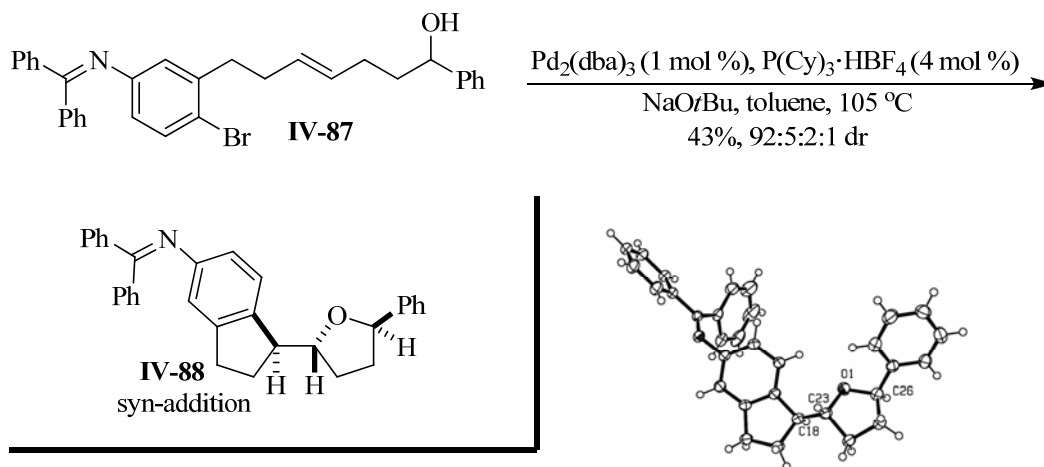
The stereochemistry of tetrahydrofuran product **IV-83** was established by X-ray crystal structure analysis of the crystalline derivative below **IV-88** (Scheme 54). The *E*- and *Z*-secondary alcohol substrates were prepared from alcohol **IV-73**, which was prepared above in Scheme 49. Alcohol **IV-73** was converted to aldehyde **IV-86** using SO₃·pyridine, and the resulting aldehyde **IV-86** was treated with phenylmagnesium bromide to afford secondary alcohol substrate **IV-87**.

Scheme 53. Preparation of Compound **IV-87**



Pd-catalyzed carboetherification of **IV-87** using catalytic $\text{Pd}_2(\text{dba})_3/\text{PCy}_3\cdot\text{HBF}_4$ afforded **IV-88** in 43% yield with 92:5:2:1 dr. Crystallographic analysis of the major diastereomer revealed syn-addition across the olefin.

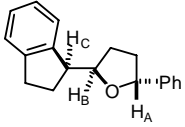
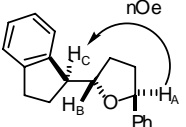
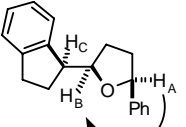
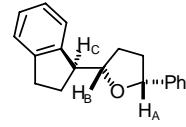
Scheme 54. Proof of Stereochemistry-Preparation and X-ray Structure of **IV-88**



The stereochemistry for the other three benzhydrylidene[1-(5-phenyltetrahydrofuran-2-yl)indan-5-yl] stereoisomers was assigned through a

combination of ^1H NMR nOe experiments and correlation of NMR spectra to those obtained for the products from cyclization of primary alcohol derivatives **IV-64** and **IV-65**. A Table of relevant NMR data for the four benzhydrylidene[1-(5-phenyltetrahydrofuran-2-yl)indan-5-yl] stereoisomers (**IV-83**, **IV-85**, **IV-83b**, and **IV-85b**) is shown below. The chemical shift of H_B was downfield in molecules bearing *trans*-thf rings (**IV-83** and **IV-85**) relative to the chemical shift of H_B in *cis*-thf-containing products **IV-83b** and **IV-85b**. The chemical shift of H_C was downfield in molecules resulting from anti-addition across the *E*-alkene (**IV-85** and **IV-85b**) relative to molecules that derive from syn-addition across the *E*-alkene (**IV-83** and **IV-83b**). In addition, nOe enhancements were observed between H_A and H_C in **IV-85** (evidence for *trans*-thf stereochemistry). The THF-ring stereochemistry of **IV-83b** was further confirmed by NMR experiments that were conducted on the product mixture obtained by the Pd/BINAP-catalyzed cyclization of **IV-57**. This transformation afforded a ~2:1 mixture of **IV-83** and **IV-83b**, with small amounts (ca 6% of total mixture) of **IV-85** and **IV-85b** also present. The resolution of the relevant signals was sufficient to observe nOe enhancements between H_A and H_B in **IV-83b** (evidence for *cis*-stereochemistry).

Table 22. Assignment of All Benzhydrylidene[1-(5-phenyltetrahydrofuran-2-yl)indan-5-yl] Stereoisomers (**IV-83**, **IV-85**, **IV-83b**, **IV-85b**)

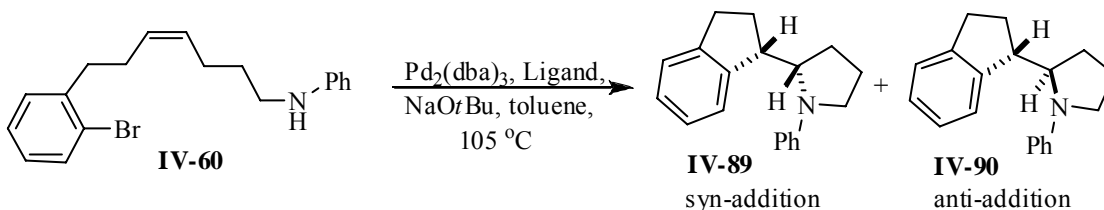
	IV-83	IV-85	IV-83b	IV-85b
	 <p><i>syn</i>-addition across <i>E</i>-alkene, <i>trans</i>-thf</p>	 <p><i>anti</i>-addition across <i>E</i>-alkene, <i>trans</i>-thf</p>	 <p><i>syn</i>-addition across <i>E</i>-alkene, <i>cis</i>-thf</p>	 <p><i>anti</i>-addition across <i>E</i>-alkene, <i>cis</i>-thf</p>
δ H _A	5.12	5.02	4.96	4.87
δ H _B	4.31	4.37	4.18	4.13
δ H _C	3.40	3.48	3.40	3.48

Intramolecular Pd-Catalyzed Carboamination Reactions

Having demonstrated the feasibility of intramolecular carboetherification reactions, we sought to determine whether intramolecular carboamination reactions could also be achieved. Thus, the *Z*-alkene substrate **IV-60** bearing a tethered aniline moiety was treated with a catalytic amount of Pd₂(dba)₃ and several different phosphine ligands under reaction conditions similar to those described above (Table 23). Interestingly, in contrast to the results obtained in cyclizations of alcohol-containing substrates, all catalysts examined for the cyclization of **IV-60** provided selectivity for formation of the (1*S**,2*S**)-stereoisomer **IV-89**, which derives from *syn*-addition across the *Z*-alkene. While the use of BINAP leads to erosion of diastereoselectivity, it does not lead to

complete reversal to the opposite diastereomer **IV-90**. As observed in the related transformations of substrates bearing alcohol nucleophiles, the major side products formed in these reactions result from debromination of the starting material (**IV-92**) or intramolecular Heck arylation (**IV-91a**, **IV-91b**) (Figure 7). Use of $\text{PCy}_3 \cdot \text{HBF}_4$ (entry 8) provided the optimal results for this transformation (88% yield, >20:1 dr) and effectively suppressed the formation of both side products. The stereochemistry in the amine series was established by X-ray crystal structure analysis of the analogous *N*-biphenyl derivatives.

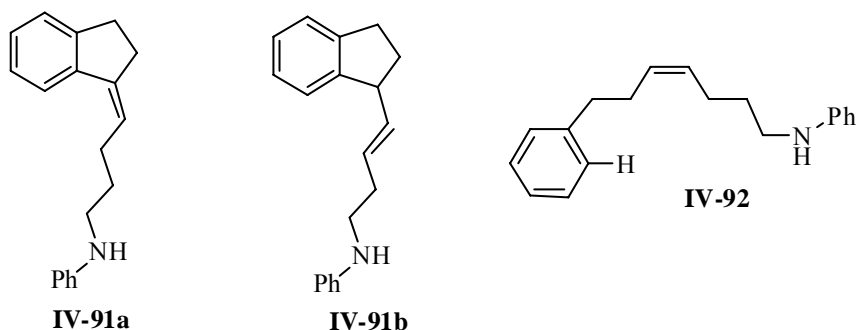
Table 23. Optimization of Carboamination Reaction of **IV-60**^{a,b}



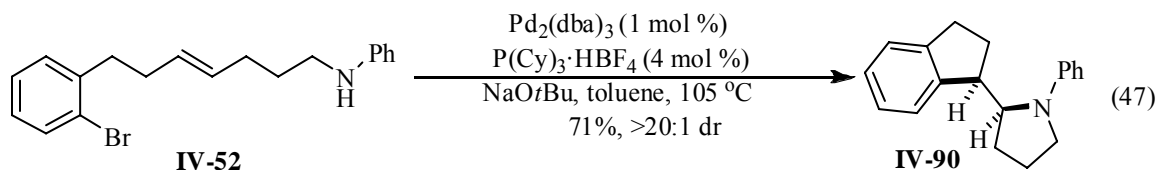
Entry	Ligand	dr (<i>syn:anti</i>)	Isolated yield
1	(±)-BINAP	1:1	46
2	DPP-Benzene	6:1	--
3	DPE-Phos	15:1	49
4	DPPE	16:1	54
5	P(<i>o</i> -tol) ₃	8:1	47
6	Xantphos	12:1	57
7	P[(<i>p</i> -MeO)C ₆ H ₄] ₃	13:1	68
8	P(Cy)₃·HBF₄	>20:1	88

^aConditions: 1.0 equiv of **IV-60**, 2.0 equiv of NaOtBu, 1 mol % Pd₂(dba)₃, 4 mol % ligand (monophosphines) or 2 mol % ligand (bisphosphines), toluene (0.1 M), 105 °C, 3-8 h.
^bDiastereoselectivities were determined by GC and/or ¹H NMR analysis of crude reaction mixtures.

Figure 7. Side Products in Pd-Catalyzed Carboamination Reactions



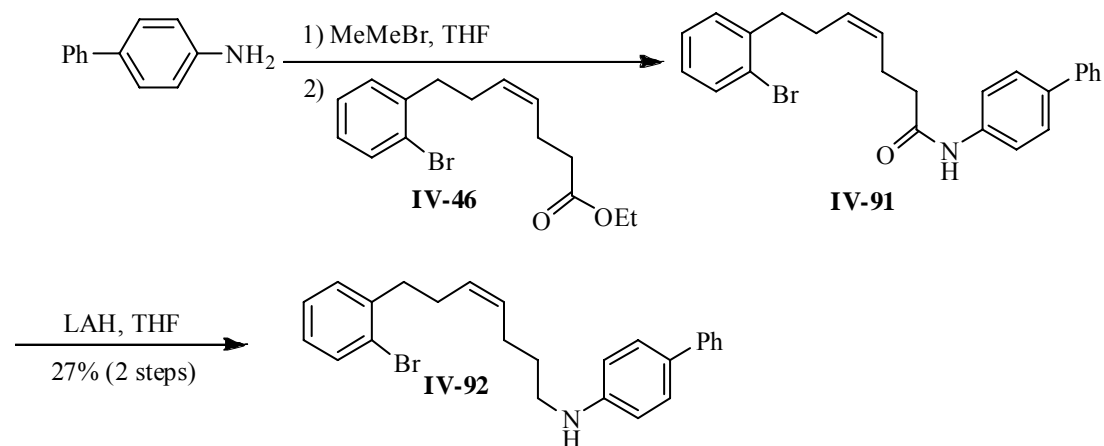
The intramolecular carboamination reactions also proved to be stereospecific, as *E*-alkene derivative **IV-52** underwent cyclization under optimized conditions to afford (1*S**,2*R**)-diastereomer **IV-90**, the product of syn-addition across the *E*-alkene, in 71% yield with >20:1 dr (eq 47). As observed with the analogous alcohol substrates, the chemical yield obtained in the reaction of the *E*-alkene was slightly lower than the yield of the reaction of *Z*-alkene **IV-60**. Reaction *E*-olefin **IV-52** with a catalyst system composed of Pd₂(dba)₃/DPP-benzene provides 6:1 selectivity for the syn-addition product.



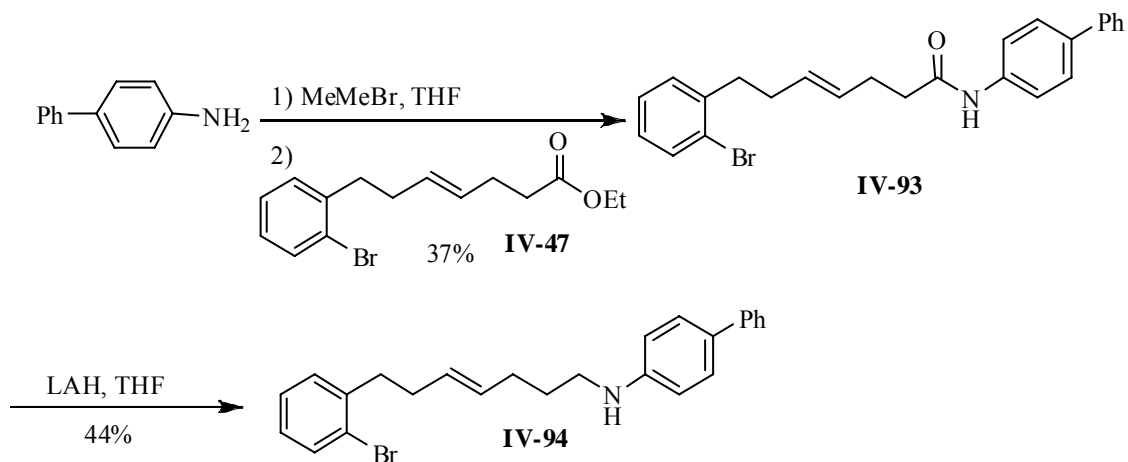
The stereochemistry of the carboamination products was determined by X-ray crystal structure analysis of the analogous biphenyl derivatives. The substrates were prepared via deprotonation of 4-aminobiphenyl with methylmagnesium bromide followed by addition of ester **IV-46** to provide amide **IV-91**. Reduction of the amide provides the

Z-olefin carboamination substrate **IV-92**. The analogous procedure was performed using *E*-ester **IV-47** to provide the *E*-olefin carboamination substrate **IV-94**.

Scheme 55. Preparation of Compound **IV-92**

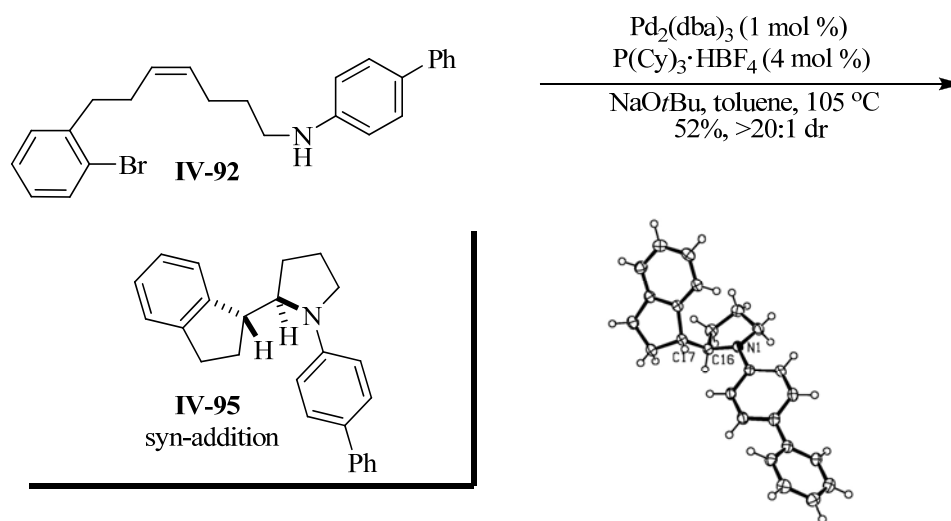


Scheme 56. Preparation of Compound **IV-94**

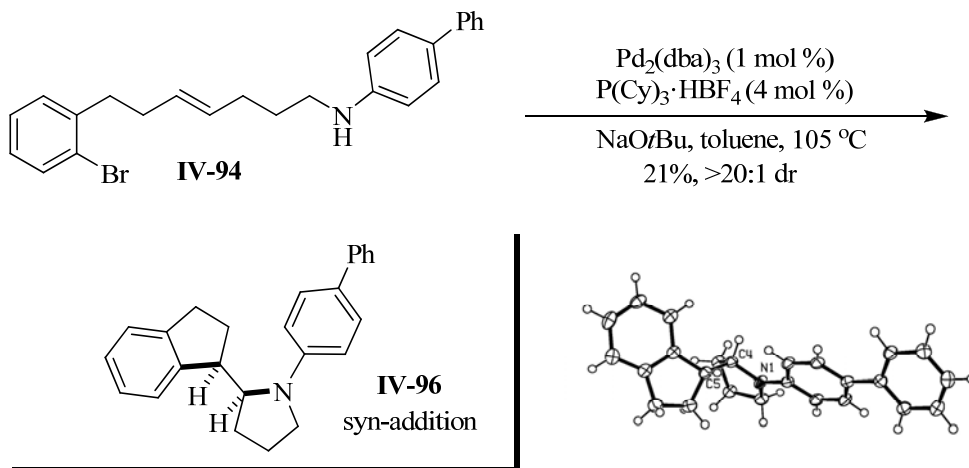


X-ray crystallographic analysis was performed on the carboamination products described above (Scheme 55 and 56) and definitively established syn-addition across the *Z*-olefin to give **IV-95** and syn-addition across the *E*-olefin to provide **IV-96**.

Scheme 57. Proof of Stereochemistry-Preparation and X-ray Structure of **IV-95**

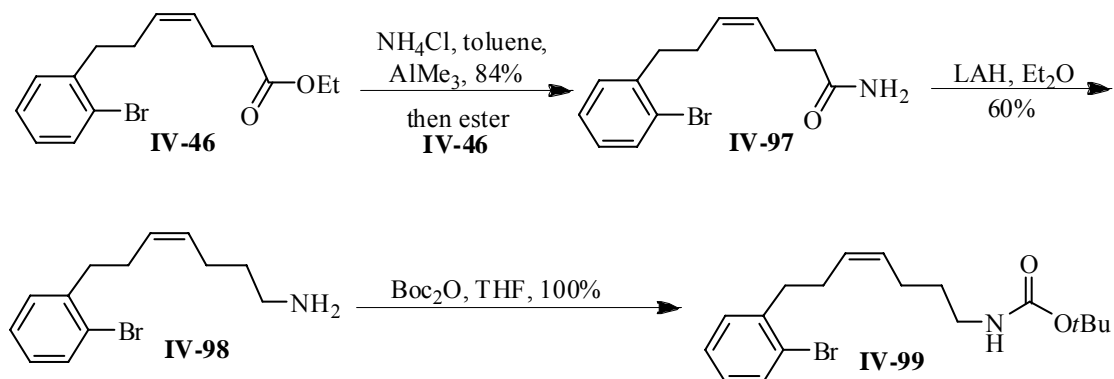


Scheme 58. Proof of Stereochemistry-Preparation and X-ray Structure of **IV-96**

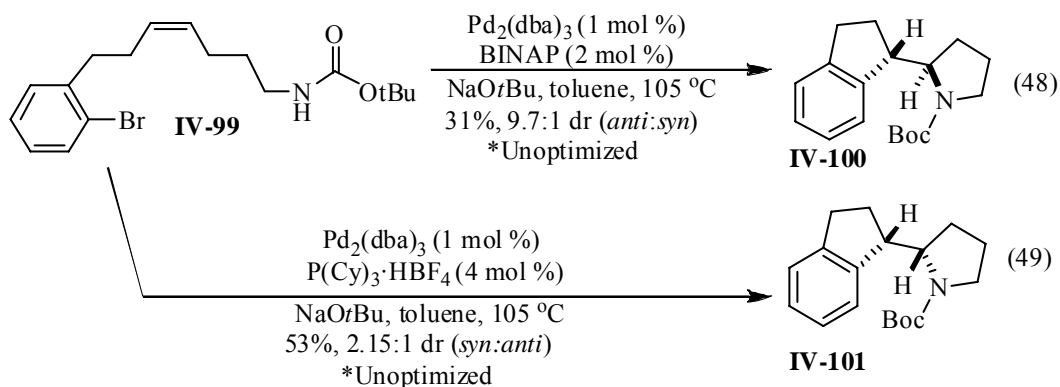


We also examined Boc-protected amines²³ in the intramolecular carboamination reactions. We prepared Boc-protected substrate **IV-99** from ester **IV-46** in three steps. Primary amide **IV-97** was prepared via treatment of ester **IV-46** with $\text{AlMe}_3/\text{NH}_4\text{Cl}$ followed by lithium aluminum hydride reduction of the resulting amide to provide amine **IV-98**. Protection of amine **IV-98** with Boc-anhydride provided the protected substrate **IV-99**.

Scheme 59. Synthesis of Boc-Amine **IV-99**

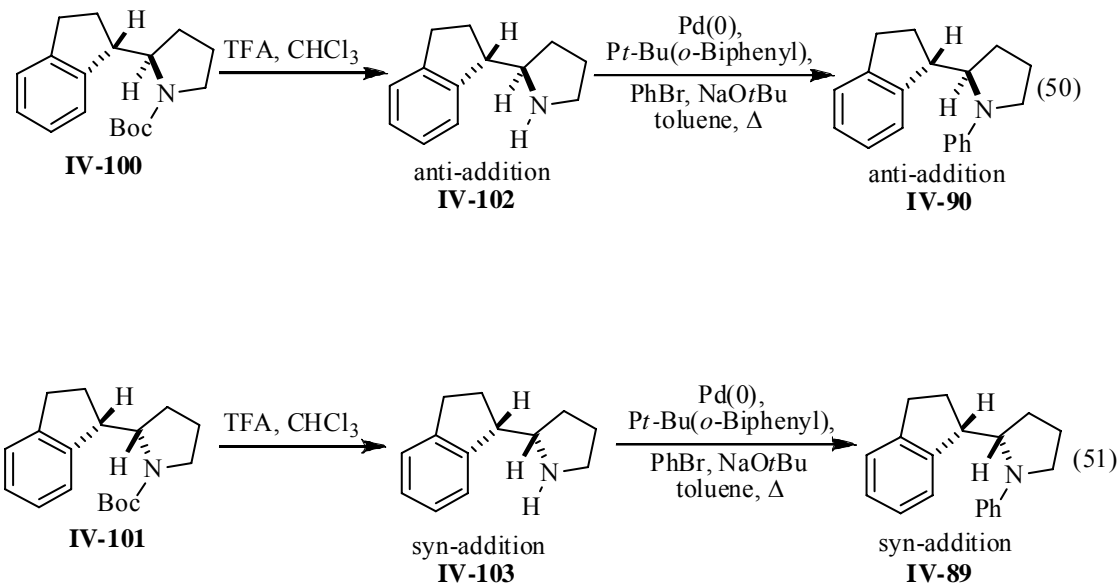


The cyclization reaction of Boc-protected amine substrate **IV-99** was conducted under two sets of reaction conditions that provide both the syn and anti-addition products in the carboetherification reactions: Pd₂(dba)₃/PCy₃·HBF₄ and Pd₂(dba)₃/BINAP. We were pleased to see that when BINAP was used as the ligand, the cyclization yields the Boc-protected pyrrolidine (anti-addition) in modest yield and good diastereoselectivity (9:1 dr), whereas when PCy₃ was used as the ligand, the syn-addition product was generated in good yield and modest diastereoselectivity (2:1 dr).

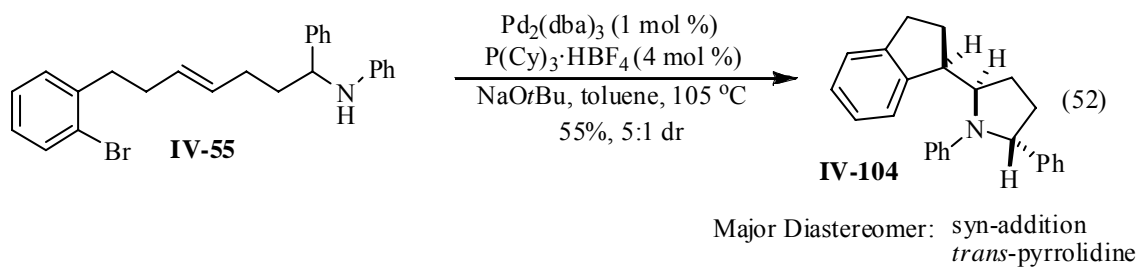


Boc-cleavage and *N*-arylation provided *N*-aryl pyrrolidines **IV-90** and **IV-89** which have already been prepared via intramolecular carboamination of the *N*-phenyl protected substrates **IV-52** and **IV-60**. However, resolution of the diastereomers on the column prohibited determination of diastereoselectivity via this method. Therefore, the diastereoselectivity was determined via GC analysis of the crude N-H pyrrolidines **IV-102** and **IV-103**. Interestingly, the diastereoselectivity in the Pd(0)/BINAP-catalyzed reaction was good (9:1 dr) and the diastereoselectivity in the Pd(0)/PCy₃ reaction was

mediocre (2:1). This result greatly contrasts from our results with the *N*-aryl pyrrolidine products, which provide high diastereoselectivity for the syn-addition product. It is likely that these reactions could be further optimized.

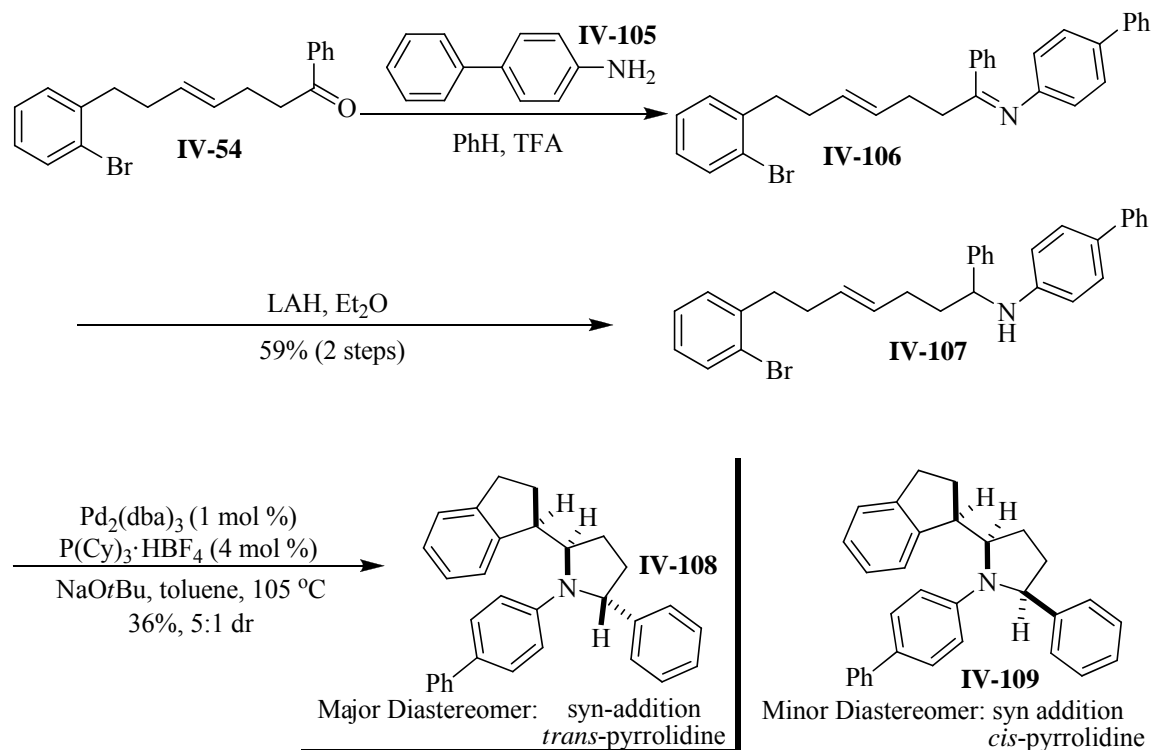


Reactions involving aniline-bearing substrates that are branched at C-1 proceeded with complete syn-selectivity. For example, treatment of *E*-alkene **IV-55** with catalytic Pd₂(dba)₃/PCy₃·HBF₄ afforded product **IV-104** in 55% yield and 5:1 diastereoselectivity (eq 52). Interestingly, the major product diastereomer was found to possess 2,5-*trans*-disubstitution around the pyrrolidine ring; the minor diastereomer results from syn-addition with *cis*-pyrrolidine formation. In contrast, the analogous intermolecular carboamination reactions of γ -(*N*-arylamino)alkenes have been shown to provide generally high selectivity for the formation of 2,5-*cis*-disubstituted pyrrolidine products.^{2a}

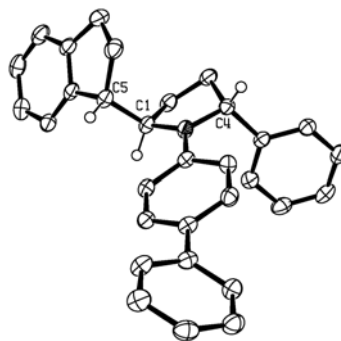


The stereochemistry was determined by synthesis and X-ray crystal structure analysis of the analogous *N*-biphenyl derivative **IV-108**. As shown in Scheme 60, this product was prepared via intramolecular carboamination of **IV-107**, which was synthesized via reduction of imine **IV-106** (prepared via reductive amination of **IV-105** with phenyl ketone **IV-54**).

Scheme 60. Preparation of **IV-107** and Proof of Stereochemistry-Preparation and X-ray Structure of **IV-108**



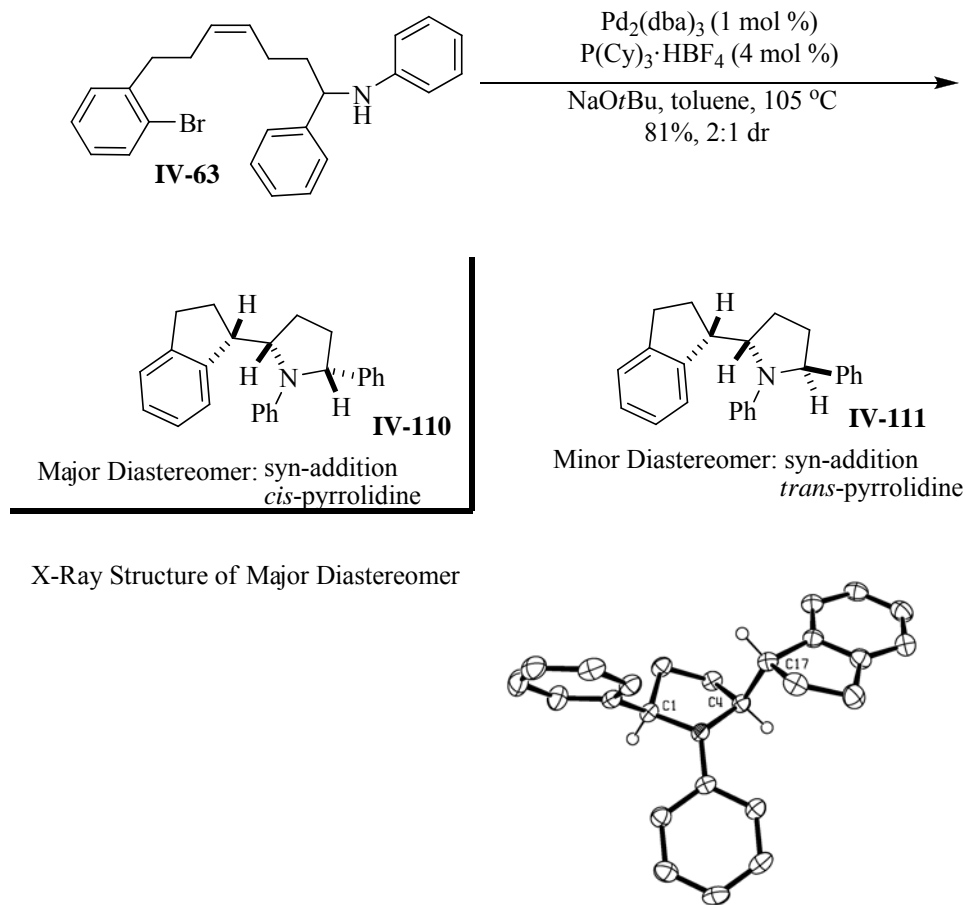
X-Ray Structure of Major Diastereomer



The reaction of *Z*-alkene **IV-63** proceeded in high yield (81%) but modest diastereoselectivity (2:1 dr) favoring product **IV-100**, which results from *syn*-addition across the alkene with *cis*-stereochemistry around the pyrrolidine ring (Scheme 61). As seen in the reaction of **IV-55** to **IV-104**, both observed diastereomers resulting from the cyclization of **IV-63** derive from *syn*-addition but differ in their relative stereochemistry

about the pyrrolidine ring. Crystallographic analysis of pyrrolidine **IV-110** confirmed the stereochemistry as shown in eq 61.

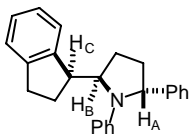
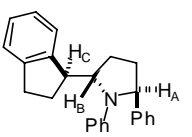
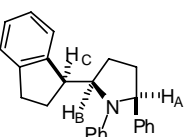
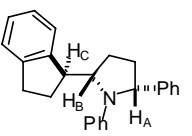
Scheme 61. Proof of Stereochemistry-Preparation and X-ray Structure of **IV-110**



The stereochemistry for *N*,5-diphenyl-2-indan-1-ylpyrrolidine stereoisomers **IV-111** and **IV-112** was assigned through correlation of NMR spectra to those obtained for **IV-104** and **IV-110**. A table of relevant NMR data for **IV-104**, **IV-111**, **IV-112**, and **IV-110** is shown below (Table 24). The chemical shift of H_B was downfield in molecules

bearing *trans*-pyrrolidine rings (**IV-104** and **IV-111**) relative to the chemical shift of H_B in *cis*-pyrrolidine-containing products **IV-112** and **IV-110**.

Table 24. Assignment of All *N*,5-diphenyl-2-indan-1-ylpyrrolidine Stereoisomers (**IV-104**, **IV-111**, **IV-112**, **IV-110**)

	IV-104	IV-111	IV-112	IV-110
	 <p><i>syn</i>-addition across <i>E</i>-alkene, <i>trans</i>-pyrrolidine</p>	 <p><i>anti</i>-addition across <i>E</i>-alkene, <i>trans</i>-pyrrolidine</p>	 <p><i>syn</i>-addition across <i>E</i>-alkene, <i>cis</i>-pyrrolidine</p>	 <p><i>anti</i>-addition across <i>E</i>-alkene, <i>cis</i>-pyrrolidine</p>
δ H _A	5.17	4.92	4.66	4.60
δ H _B	4.87	4.51	4.39	4.05
δ H _C	4.14	4.19	3.95	3.49

Reactivity and Stereoselectivity

The intramolecular palladium-catalyzed carboetherifications and carboaminations of γ -hydroxy- or γ -aminoalkenes with tethered aryl bromides provides a new, stereoselective means to generate carbocycles bearing attached heterocycles. These reactions effect the conversion of acyclic precursors to bicyclic products with formation

of two bonds, two rings, and two stereocenters in a single step. The yields and selectivities are dependent on a number of factors, but under optimal conditions the desired products are obtained in moderate to good yields with good to excellent stereocontrol. Several trends in reactivity have been observed during the course of these experiments. From the results described above, it appears that the chemical yield is affected by the alkene geometry, the nature of the heteroatom, and the degree of substitution adjacent to the heteroatom. For example, substrates bearing *Z*-alkenes are usually transformed in higher chemical yield than the analogous *E*-alkenes. In addition, reactions involving starting materials with tethered aniline nucleophiles produce higher yields than analogous reactions of alcohol bearing substrates (with a similar degree of substitution). Finally, in many cases substitution next to the heteroatom decreases the chemical yield. The stereochemical outcome of these reactions is influenced by both the nature of the heteroatom and the catalyst. All substrates containing nitrogen nucleophiles that were examined in these studies are selectively converted to products resulting from syn-addition across the double bond. Although the catalyst structure has an effect on the diastereoselectivity of the pyrrolidine-forming reactions, with diastereomeric ratios varying from 1:1 to >20:1, no catalyst examined led to selective formation of the anti-addition product. In contrast, primary and tertiary alcohol substrates were transformed to products of syn-addition when catalysts bearing electron-rich monodentate ligands such as PCy₃, PMe₃, or P[(*p*-MeO)C₆H₄]₃ were employed, but reactions of these starting materials gave products of anti-addition when chelating phosphines with small bite angles (e.g., BINAP, DPP-benzene, or DPPE; bite angles $\leq 93^\circ$) were used as supporting ligands. Notably, in carboetherification reactions of primary and tertiary alcohols either

product diastereomer could be obtained selectively from either starting alkene stereoisomer. Reactions involving α -substituted alcohols catalyzed by Pd/PCy₃ or P[(p-MeO)C₆H₄]₃ proceed with good to excellent levels of selectivity for the formation of one of four possible diastereomeric products; the major diastereomer results from syn-addition with *trans*-THF formation. However, use of Pd/BINAP with these substrates leads to low yields and modest selectivities. The analogous Pd/PCy₃-catalyzed reactions of α -branched anilines proceed in good yields with very high syn-selectivity, but give mixtures of *cis*- and *trans*-pyrrolidine products.

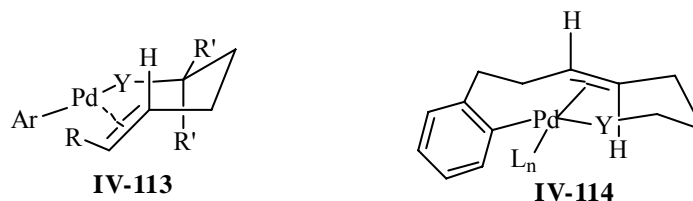
Mechanism of Intramolecular Carboetherification Reactions

That Provide syn-Addition Products

In our previous studies on intermolecular Pd-catalyzed carboetherification and carboamination reactions, we obtained results that were most consistent with a mechanistic pathway involving syn-insertion of the alkene moiety into the Pd-heteroatom bond of intermediate Pd(Ar)(OR) or Pd(Ar)(NRR') complexes (e.g. **IV-113**, Figure 8).² Other mechanistic scenarios such as product formation via a Wacker type anti-addition or via intermolecular carbopalladation followed by C–O or C–N bond-forming reductive elimination were ruled out on the basis of the observed product stereochemistry, the side products formed in the reactions, and the high regioselectivity for formation of five-membered ring products. The fact that syn-addition products are also obtained in the intramolecular reactions suggests that a similar mechanism may operate. However, this pathway would necessitate the formation of 11-membered ring intermediates (e.g. **IV-114**, Figure 8), which may be entropically unfavorable, and would require transannular

alkene insertion of a macrocyclic palladacycle bearing an internal alkene, which is unprecedented.²⁴ Thus, two plausible mechanisms for the formation of the observed syn-addition products of intramolecular reactions merit consideration.

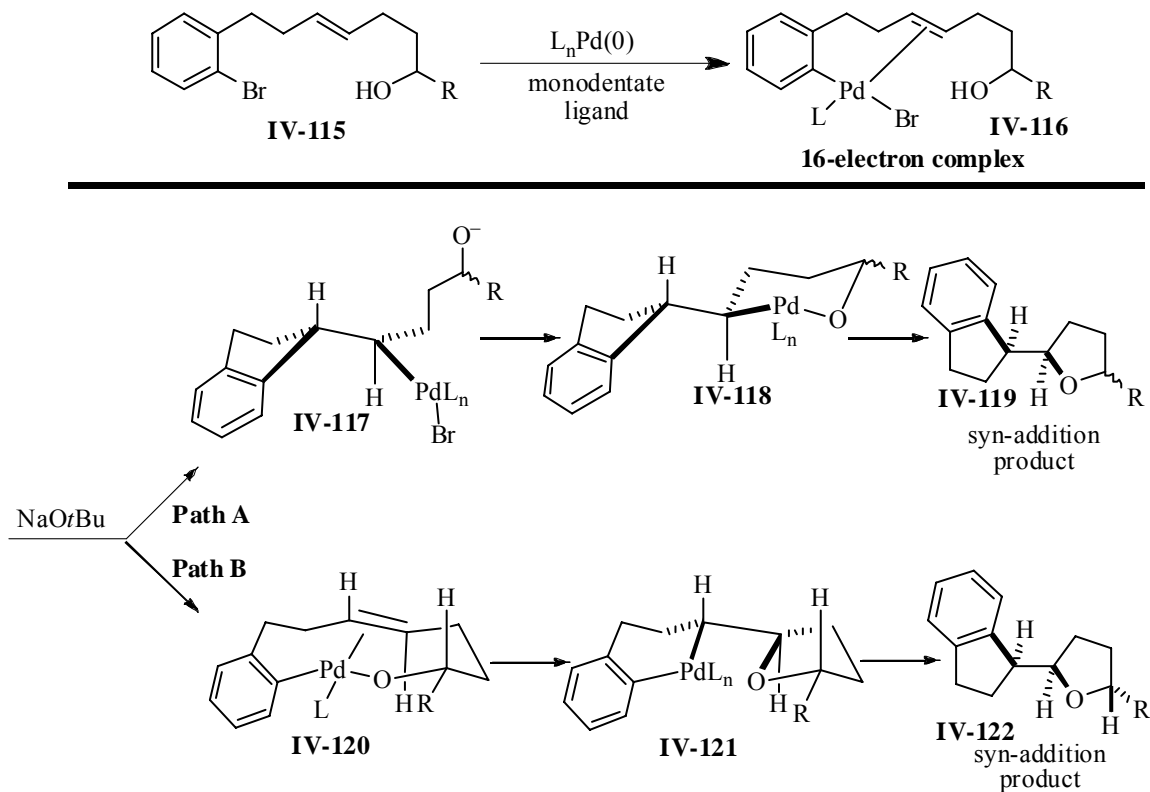
Figure 8. Comparison of Intermolecular and Intramolecular Systems



As shown in Scheme 62, oxidative addition of the aryl bromide **IV-115** to the $L_nPd(0)$ species generated in situ from $Pd_2(dba)_3$ and a monodentate phosphine ligand, followed by coordination of the tethered alkene, would afford the 16-electron intermediate **IV-116**, a species common to both mechanistic scenarios. This intermediate could potentially be converted to the observed products via a Heck-type 5-exo carbopalladation²⁴ and deprotonation by $NaOtBu$ to provide **IV-117** (Path A), which could undergo nucleophilic displacement of the bromide by the tethered alkoxide to afford **IV-118**.²⁵ An unprecedented sp^3 carbon–oxygen bond-forming reductive elimination from Pd(II) complex **IV-118** (with retention of configuration) would generate the observed product **IV-119**.^{26,27} However, the fact that the cyclizations of secondary alcohol substrates **IV-49** and **IV-57** proceed with good to excellent stereoselectivity for *trans*-tetrahydrofuran formation and syn-addition suggests that this pathway is unlikely. If the reactions proceed via the mechanism outlined in Path A, the 5-exo carbopalladation event would determine both the syn/anti-stereochemistry as well as the stereochemistry

around the THF ring. If the stereochemistry-determining event occurs via intramolecular carbopalladation of intermediate **IV-116** with no communication between the alcohol and the metal, it is unlikely that high selectivity for *trans*-THF formation would be observed. A mechanism involving fast and reversible carbopalladation followed by selective Pd heteroatom bond formation of one possible diastereomeric intermediate could also account for the high diastereoselectivity. However, reversible carbopalladation reactions have only been observed in complexes lacking β -hydrogen atoms; carbopalladation is believed to be irreversible in most other systems. The fact that oxidized/reduced side products are observed instead of Heck-type side products also suggests this pathway is less plausible than Path B.²⁸ In addition, Heck-type side products that would result from slow reductive elimination following the 5-exo carbopalladation are not formed in significant amounts in optimized reactions that lead to the syn-addition product.

Scheme 62. Rationale for Syn-Addition Products

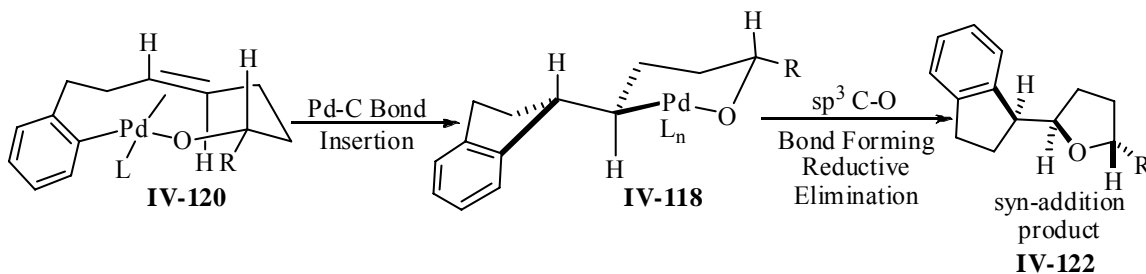


In contrast, the mechanistic pathway outlined in Scheme 62, Path B, which is analogous to that proposed for the intermolecular reactions,² can account for both high syn-selectivity and high selectivity for *trans*-THF formation. In this scenario, the 16-electron intermediate **IV-116** could undergo deprotonation followed by associative ligand substitution²⁹ of the alkoxide for the bromide to afford 11-membered palladacycle **IV-120** in which the alkyl group is oriented in the pseudoequatorial position. The vast majority of ligand substitutions at 16-electron Pd(II) complexes proceed via an associative mechanism. The very rare examples of dissociative ligand substitution at 16-electron Pd(II) complexes involve the extremely bulky, monodentate, and unusually labile ligands tris(2,4,6-trifluoromethylphenyl)phosphine and $P(o\text{-tol})_3$. Formation of the

11-membered palladacycle **IV-120** is presumably facilitated by complexation of the alkene to the metal, which allows for Pd–O bond formation via an effectively smaller ring. Transannular insertion of the alkene into the palladium-oxygen bond would generate **IV-121**, which could undergo C–C bond-forming reductive elimination to form the observed product **IV-122**. Pseudoequatorial orientation of the α -substituent in the transition state for alkene insertion would lead to the observed products bearing *trans*-2,5-disubstituted tetrahydrofuran groups and should be lower in energy than the related transition state with axial orientation of the α -group due to developing transannular interactions. The side products that comprise the remainder of the mass balance in these reactions result from oxidation of the alcohol with concomitant reduction of the aryl bromide and are consistent with competing β -hydride elimination of **IV-120** prior to alkene insertion.

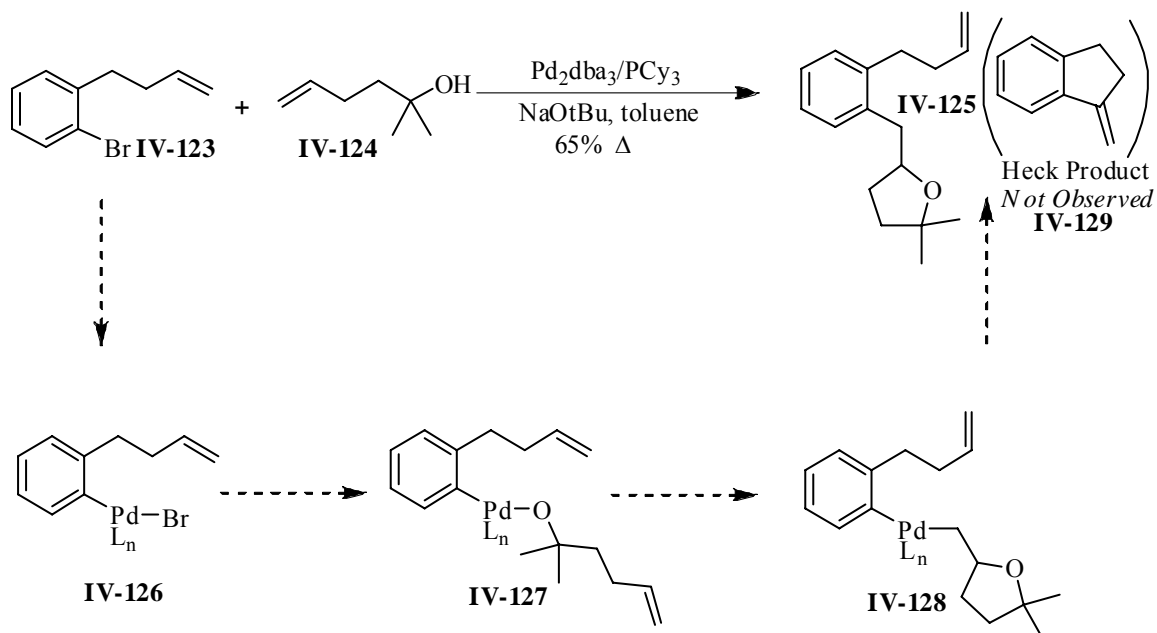
The experiments described above cannot rule out another possible mechanism for product formation that would provide **IV-122** via alkene insertion into the Pd–C bond of macrocycle **IV-120** (Scheme 63). However, literature precedent suggests that alkene insertion into the metal–heteroatom bond of late-metal M(R)(OR) complexes is usually more facile than insertion into the M–C bond.^{2,30,31}

Scheme 63. Alternate Mechanism for Syn-Addition Products (Pd–C Bond Insertion)



In order to further probe the relative rates of C–O bond insertion versus C–C bond insertion, a simple experiment was designed. The aryl bromide **IV-123** was synthesized via Wittig olefination of aldehyde **IV-44**. Treatment of **IV-123** with alcohol **IV-124**, NaOtBu, and catalytic Pd₂(dba)₃/PCy₃ afforded tetrahydrofuran **IV-125** as the sole product. The carbocycle **IV-129** which would result from intramolecular Heck reaction of **IV-123**, was not observed under these reaction conditions as determined by ¹H NMR analysis. This suggests that intramolecular carbopalladation (Pd–C bond insertion) is slow relative to the rate of Pd-alkoxide formation and oxypalladation (Pd–O bond insertion) under the reactions conditions described above. This provides further support for the Path B (Scheme 62) described above.

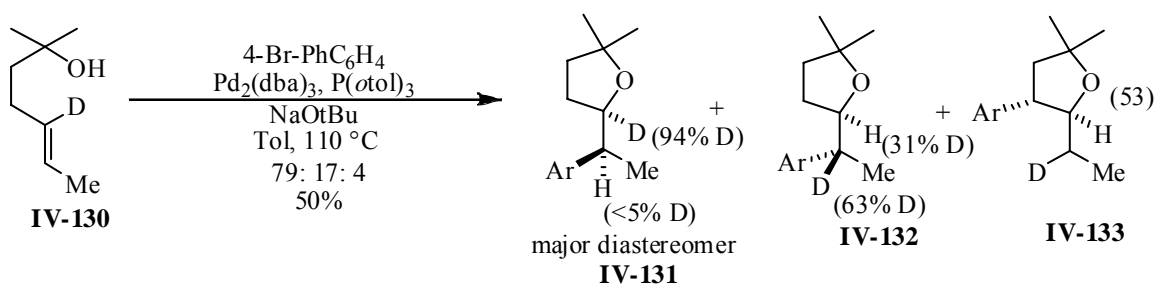
Scheme 64. Intermolecular Probe: Rate of Pd–C vs. Pd–O Bond Insertion



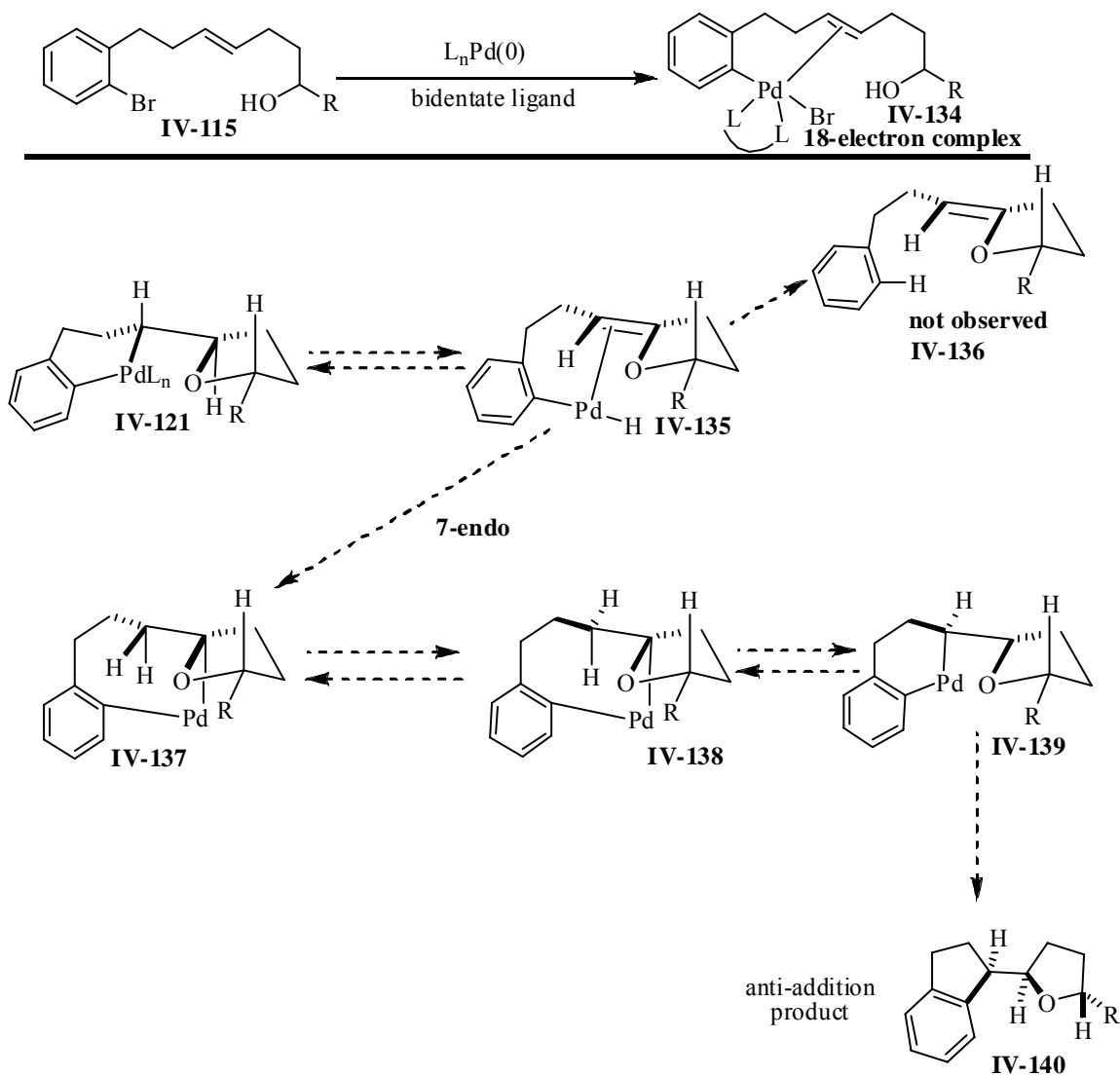
Mechanism of Intramolecular Carboetherification Reactions That Provide anti-Addition Products

In contrast to all previously described intermolecular carboetherification reactions of internal alkenes with aryl bromides,^{2,32,33,34} which provide syn-addition products, the intramolecular carboetherifications provide products resulting from anti-addition when chelating ligands with small bite angles (e.g., BINAP or DPP-benzene) are employed. Our group has previously shown that anti-addition products observed in intramolecular carboetherification reactions are actually generated through syn-oxypalladation followed by reversible β -hydride elimination/reinsertion/ σ -bond rotation processes. This was established through deuterium labeling experiments (Scheme 53) which established that the deuterium migration in the minor diastereomer was consistent with palladium migration occurring after the key oxypalladation event.^{2f} However, formation of anti-

addition products in the intramolecular reactions described in this chapter are unlikely as this pathway would require a 7-endo-hydridopalladation of an aryl-(hydrido)palladium alkene complex (**IV-135**), which is energetically unfavorable.³⁵ Endo carbopalladation reactions are extremely rare, and 7-endo hydridopalladation reactions are unknown. In addition, side products that would result from reductive elimination of **IV-135** prior to 7-endo-hydridopalladation are not observed; the major side products in reactions that afford anti-addition products derive from intramolecular Heck-type reactions (Scheme 65).



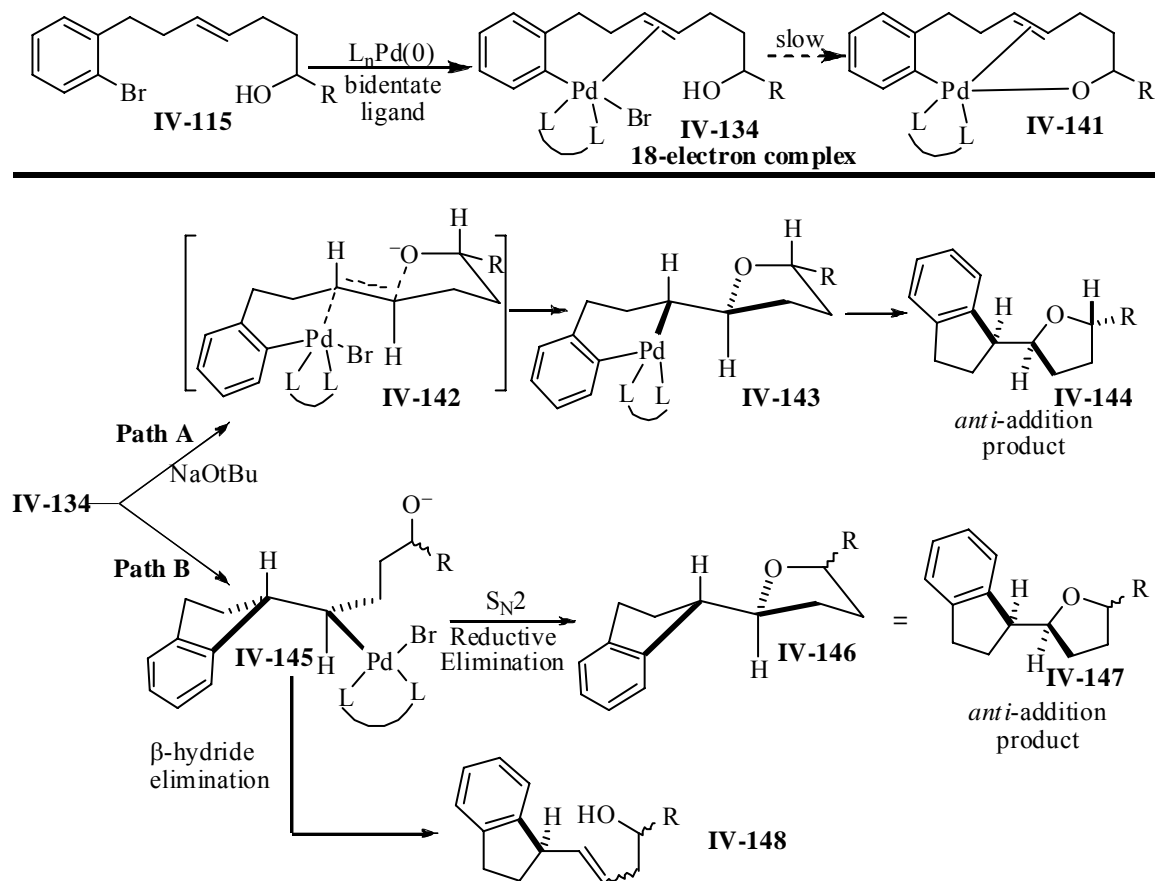
Scheme 65. Formation of Anti-Addition Products from β -Hydride Elimination/Reinsertion/ σ -Bond Rotation Pathway



Instead, it appears likely that the change in observed product stereochemistry arises from a fundamental change in the mechanism through which the products are formed. This change can be attributed to the notion that tightly chelating ligands are expected to inhibit the associative ligand substitution process required for palladium alkoxide formation.²⁹ As outlined in Scheme 66, Path A, oxidative addition of the aryl

bromide **IV-115** to a (L–L)Pd(0) complex followed by alkene coordination would generate 18-electron complex **IV-134**. This coordinatively saturated complex could not be converted to a palladium(aryl)(alkoxide) analogous to **IV-141** via an associative ligand substitution process, and it is unlikely that the 11-membered palladacycle **IV-141** would be generated in the absence of alkene coordination, as 11-membered ring formation is entropically unfavorable. Thus, conversion of **IV-115** to **IV-141** is likely to be relatively slow. Conversion of **IV-134** to **IV-141** could occur via dissociation of one arm of the chelating ligand followed by associative substitution of alkoxide for bromide, or by dissociation of the bromide followed by associative ligand substitution. Either of these pathways is likely to be higher in energy than the analogous conversion of **IV-116** to **IV-120**. Instead, a mechanistic pathway involving a Wacker-type anti-alkoxypalladation may be more accessible in this system than in other carboetherification processes. The anti-alkoxypalladation of **IV-134** via an ordered transition state such as **IV-142** could generate **IV-143**, which would provide anti-addition product **IV-144** upon C-C bond-forming reductive elimination. The stereochemistry around the tetrahydrofuran ring would again be dictated by nonbonding interactions in the transition state, with a preference for pseudoequatorial orientation of substituents. However, prior studies have shown that differences in transition-state energies for pseudoaxial versus pseudoequatorial orientation of the α -substituents or the alkene moiety in related Wacker-type cyclizations may be relatively small, as the preference for *trans*-THF formation is often modest in the absence of additional substituents.^{10b}

Scheme 66. Formation of Anti-Addition Products: Wacker and Heck-Type Mechanisms



Alternatively, the products of anti-addition could derive from Heck-type carbopalladation of **IV-134** to generate **IV-145**, followed by C–O bond-forming reductive elimination through an S_N2 mechanism, which would lead to inversion of the C2 stereocenter to provide **IV-147** (Scheme 66, Path B). Although we cannot rule out product formation via this mechanism, we currently favor the hypothesis involving a Wacker-type anti-oxypalladation pathway, as the sp^3 C–O bond-forming reductive elimination required for product formation via Path B is not known to occur from Pd(II) complexes^{26,27} and would require S_N2 substitution to occur at a hindered secondary

carbon atom flanked by an adjacent secondary carbon stereocenter. The fact that Heck-type side products (e.g., **IV-148**) are generated in these transformations suggests that complex **IV-148** is kinetically accessible, but mechanistic Pathway B cannot account for control of relative stereochemistry around the tetrahydrofuran ring. The observed selectivity for formation of *trans*-disubstituted tetrahydrofuran products in the Pd/BINAP-catalyzed reaction of **IV-115** is more consistent with an ordered transition state similar to **IV-142**. Thus, although **IV-145** may be accessible under the reaction conditions, it is not necessarily an intermediate along the pathway between **IV-115** and **IV-144**.

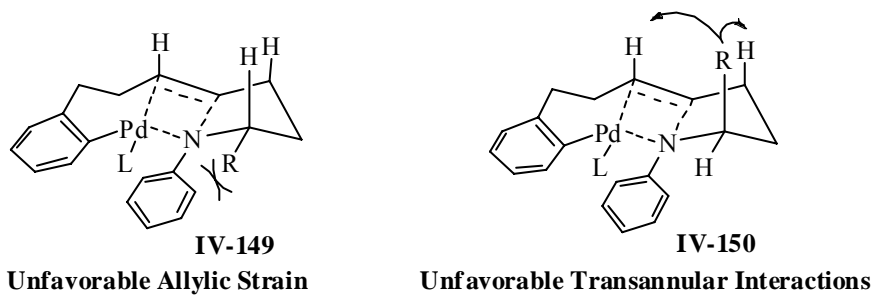
Mechanism and Stereochemistry of Intramolecular Carboamination

Reactions

The intramolecular carboamination reactions described above provide products that derive from *syn*-addition of the amine and the arene across the carbon-carbon double bond. It is likely that these transformations proceed via a mechanism similar to that outlined above (Scheme 62, Path B) for *syn*-addition reactions of alcohol substrates, which involves a transannular alkene insertion of an 11-membered palladium-(aryl)(amido) intermediate through transition state **IV-149** or **IV-150**. However, in reactions of substrates bearing tethered anilines with α -stereocenters, the factors leading to a preference for either *trans*-pyrrolidine stereochemistry (*E*-alkenes) or *cis*-pyrrolidine stereochemistry (*Z*-alkenes) are more complicated than in the related transformations of secondary alcohols, and the origin of the observed stereochemistry is not entirely clear. One possible explanation for these results is that pseudoequatorial orientation of the C1–

R-group (**IV-149**) would minimize developing transannular interactions in the transition state,³⁶ but could lead to developing $A^{(1,3)}$ -strain between the Nsp^2 aryl group and the pseudoequatorial R-substituent.³⁷ Alternatively, pseudoaxial orientation of the R-group (**IV-150**) may minimize allylic strain at the expense of increased unfavorable transannular interactions. The results of the experiments shown in eq 52 and Scheme 61 are consistent with preferred pseudoequatorial orientation of the substituent when the substrate contains the *E*-alkene geometry, which suggests that the energetic effects of the transannular interactions outweigh the effects of $A^{(1,3)}$ -strain for this system. In contrast, there appears to be a slight preference for pseudoaxial orientation with the *Z*-alkene geometry, which implies that the transannular interactions may be lessened relative to the degree of allylic strain in this case.³⁸

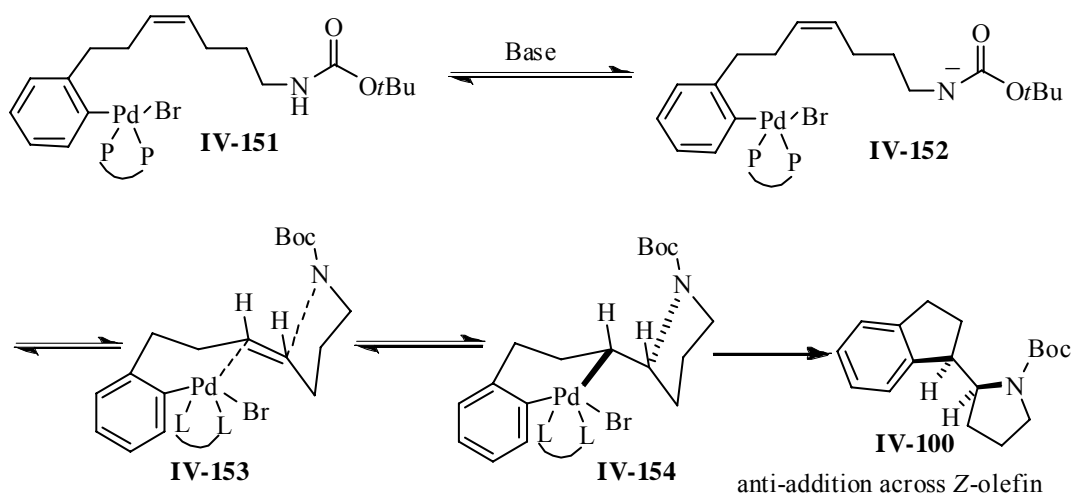
Figure 9. Allylic Strain and Transannular Interaction in Pd-Amido Macrocycle



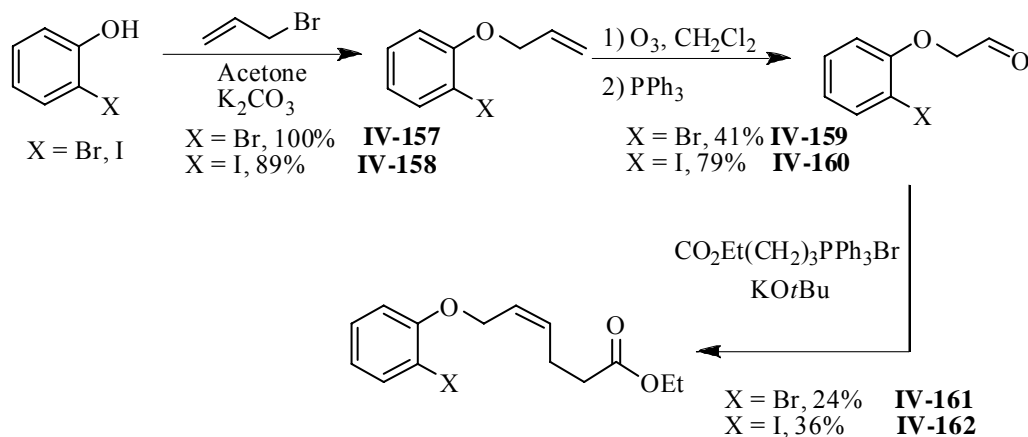
In contrast to Pd/BINAP or Pd/DPP-benzene-catalyzed reactions of alcohol substrates, which provide good selectivity for products of anti-addition, use of BINAP or DPP-benzene with substrates bearing aniline nucleophiles results in low *syn*/*anti* stereoselectivity. The differences in the stereochemical outcome of these transformations may be due to the effect of heteroatom nucleophilicity (anionic alkoxide versus neutral

amine) on the rate of anti-heteropalladation. In the presence of NaOrBu there is likely a significant equilibrium concentration of highly nucleophilic alkoxides that results from deprotonation of the substrate alcohol.³⁹ In contrast, deprotonation of the less acidic aniline nucleophile would occur to a lesser extent, and hence the concentration of anilide anion is likely to be low, which may result in relatively slower rates of Wacker-type addition of the nitrogen nucleophiles. The fact that yields of anti-addition products of intramolecular carboetherification reactions decrease (under identical conditions) with increasing steric bulk of the alcohol nucleophile is also consistent with this notion, as is the observation that substrate **IV-99** bearing an *N*-Boc group was selectively converted to anti-addition product with catalytic Pd₂(dba)₃/BINAP.⁴⁰ The pK_a of the carbamate is considerably lower than that of the aniline and a sufficient amount of anionic nitrogen is presumably present to facilitate anti-aminopalladation in this system (Scheme 67).

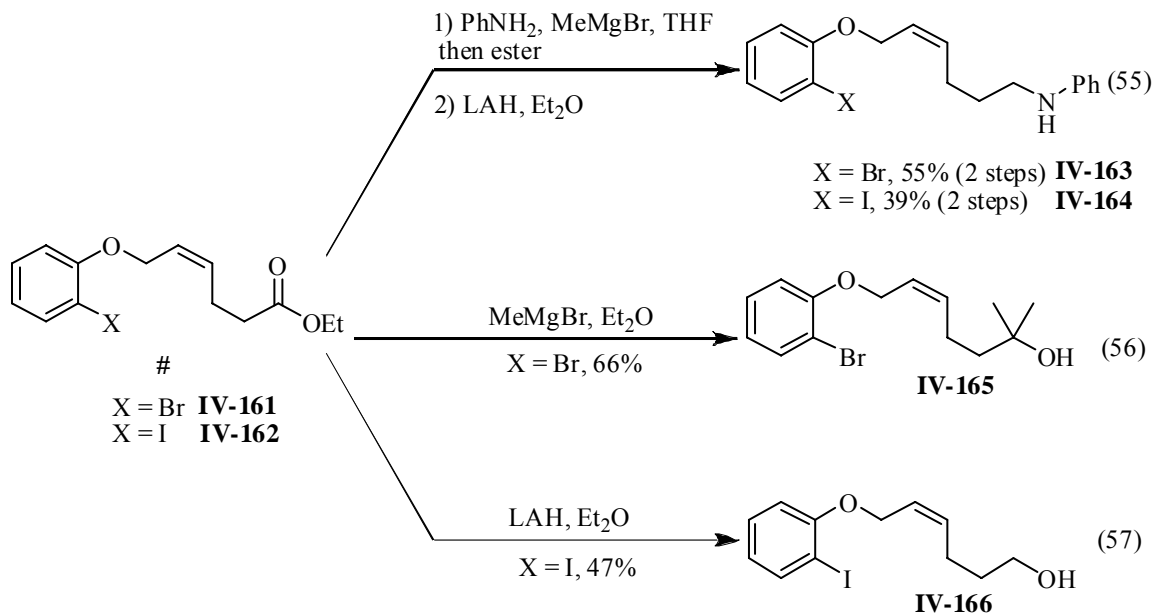
Scheme 67. Anti-Amino-Palladation for the Synthesis of Boc-Protected Pyrrolidines



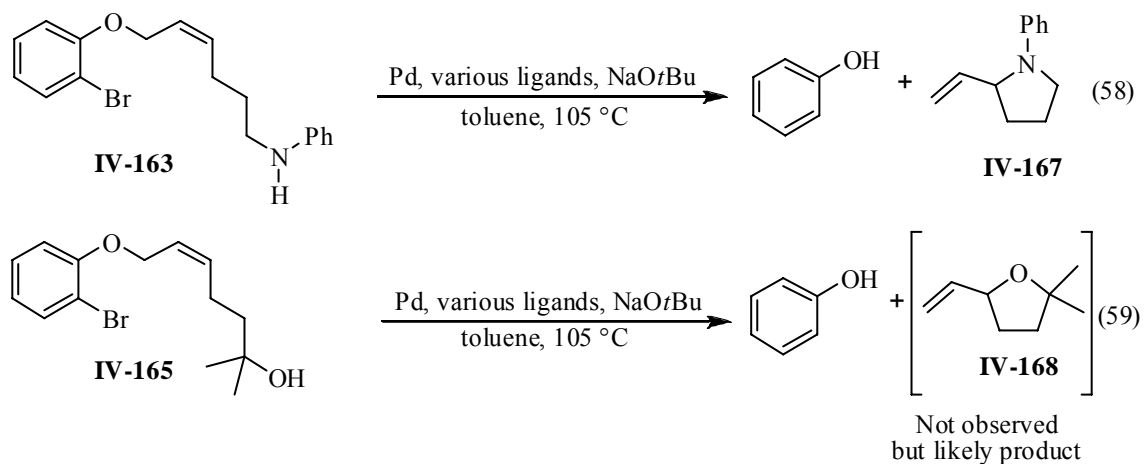
Scheme 68. Substrate Synthesis of Esters **IV-161** and **IV-162**



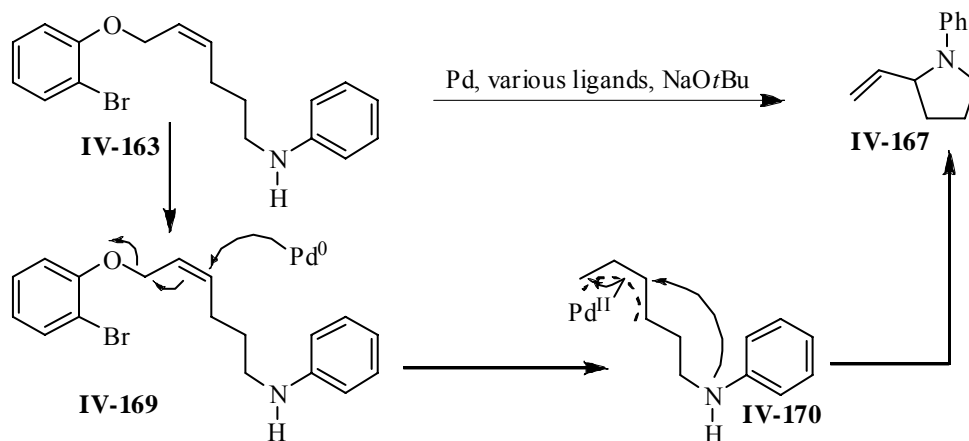
Esters **IV-161** and **IV-162** were converted to amines and alcohols **IV-163-IV-166** using a sequence of reactions analogous to those employed for conversion of simple substrates (Scheme 44-47). Conversion of ester **IV-161** to the *N*-phenyl amide, followed by lithium aluminum hydride reduction provided amines **IV-163** and **IV-164**. Ester **IV-161** was converted to tertiary alcohol **IV-165** via addition of methylmagnesium bromide. Reduction of ester **IV-162** with lithium aluminum hydride provides alcohol **IV-166**.



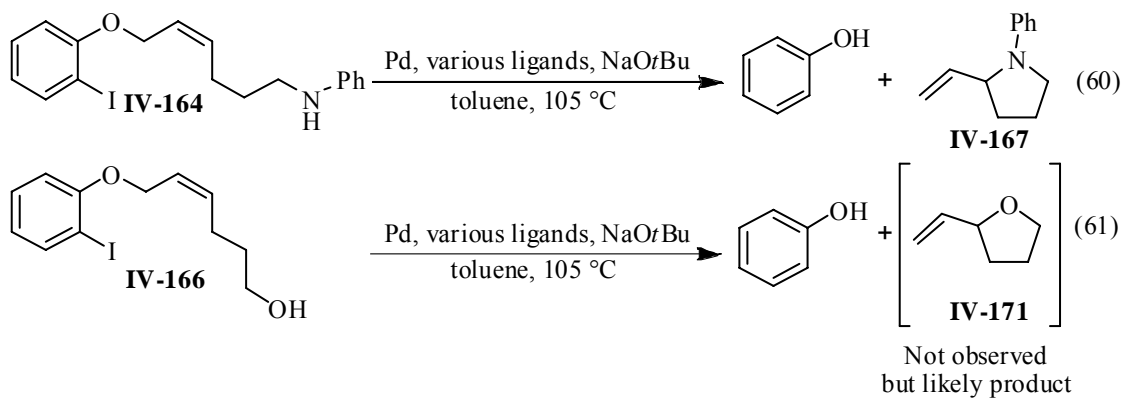
The carboamination and carboetherification of substrates **IV-163** and **IV-165** were examined using standard reaction conditions with various different ligands. In the attempted carboamination reaction of **IV-163**, vinyl pyrrolidine **IV-167** was isolated rather than the desired product. Presumably formation of the volatile vinyl tetrahydrofuran **IV-168** also occurs in the related carboetherification of **IV-165**, as only phenol was observed by ^1H NMR analysis of crude reaction mixtures. Vinyl pyrrolidine **IV-167** likely arises from nucleophilic attack of the amine nucleophile on the π -allyl palladium complex **IV-169** that results from oxidative addition of Pd(0) to **IV-163** as shown in Scheme 69.



Scheme 69. Formation of **IV-167** Via Decomposition of **IV-163**

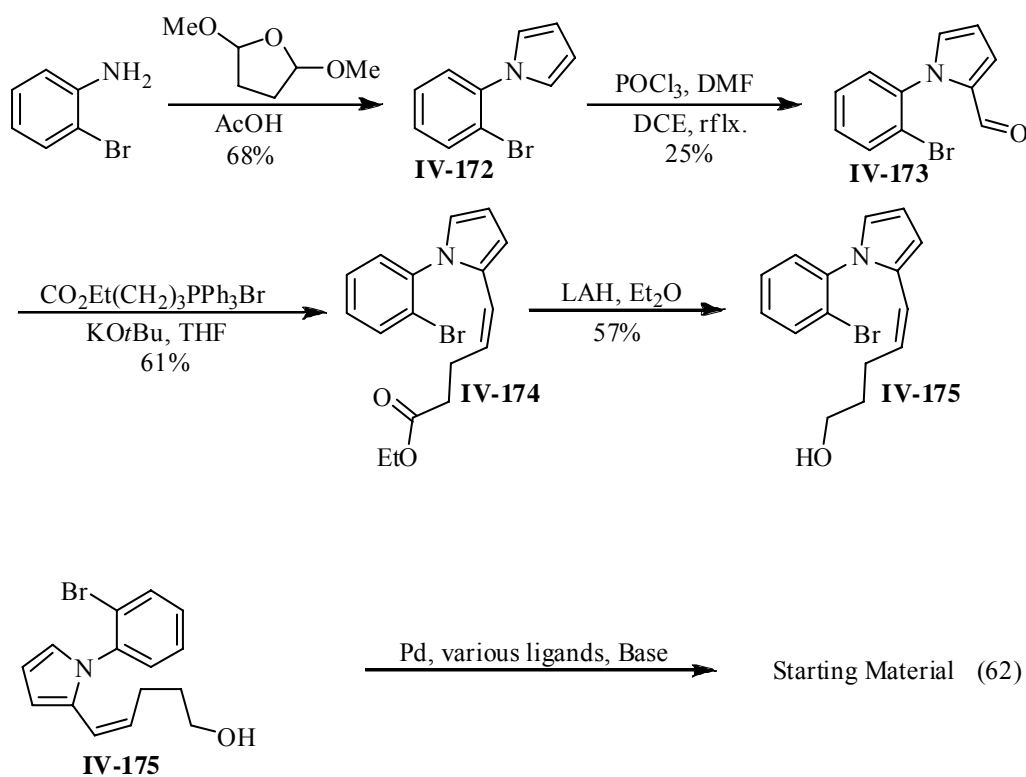


We felt that the cyclization could be facilitated by substituting an iodide for the bromide on the arene, since the rate of oxidative addition is faster with iodides relative to bromides. However, upon subsection of amine substrate **IV-164** to the carboamination conditions, vinyl pyrrolidine **IV-167** was again formed. Attempted carboetherification of substrate **IV-166** also generated phenol as the only observed product. Conducting the reactions at lower temperatures did not lead to improved results.



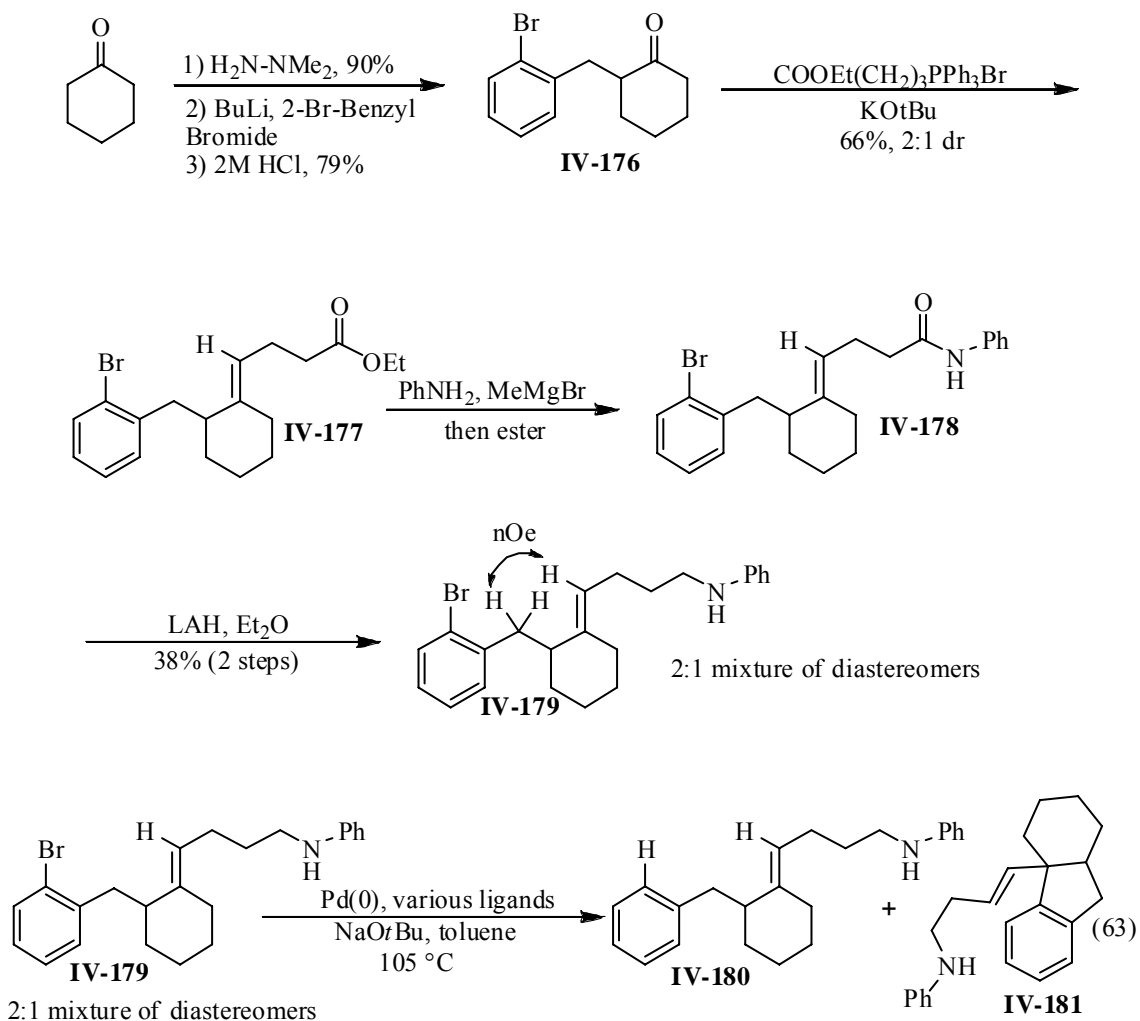
We briefly examined the carboetherification of heterocycle-containing substrates such as pyrrole **IV-175**, which was prepared in 4 steps from 2-bromoaniline. As shown below, reaction of 2-bromoaniline with 2,5-dimethoxyfuran provides pyrrole **IV-172**. Formylation provides aldehyde **IV-173**, which undergoes Wittig olefination to afford ester **IV-174**. Lithium aluminum hydride reduction generates alcohol substrate **IV-167**. Unfortunately, all attempts to cyclize this substrate resulted in no reaction and starting material was recovered unchanged (eq 62).

Scheme 70. Synthesis of IV-175



We also examined the intramolecular carboamination reaction of cyclohexanone-derived trisubstituted olefin substrate **IV-179**, which was prepared in 4 steps from cyclohexanone. As shown below, *N,N*-Dimethylhydrazine was condensed with cyclohexanone followed by deprotonation and alkylation with 2-bromobenzyl bromide. Wittig reaction of **IV-176** with the ylide generated from reaction of 4-ethoxy-4-oxobutyl triphenylphosphonium bromide with potassium *tert*-butoxide provides **IV-177** as a 2:1 mixture of diastereomers. The stereochemistry of the major diastereomer was assigned by NOESY-2D analysis of the major diastereomer. The ester was then treated with the anion of aniline to provide **IV-178** which was then reduced with lithium aluminum hydride. Unfortunately, the attempted carboamination of amine **IV-179** under standard conditions provided a mixture of the reduction of the starting material **IV-180** as well as Heck product **IV-181** (eq 63).

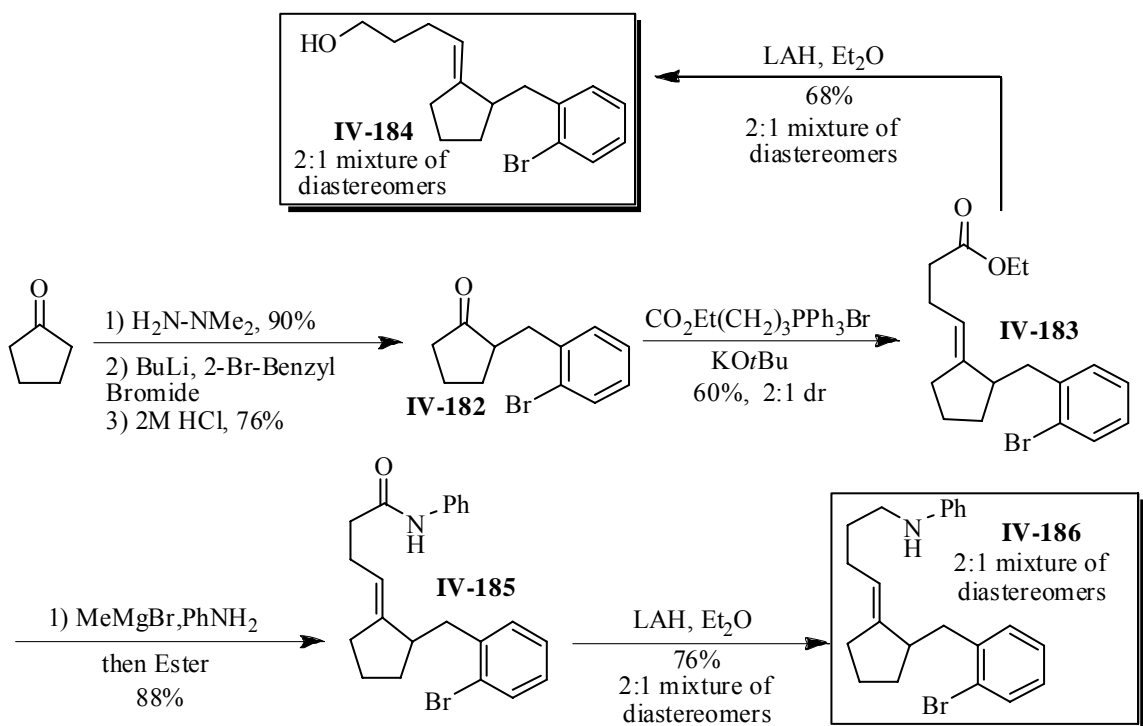
Scheme 71. Synthesis of IV-179



Although, the reaction of cyclohexanone derivative **IV-179** was unsuccessful, the analogous intramolecular carboamination reaction of cyclopentanone-derived trisubstituted olefin substrate **IV-186**, which was prepared in 4 steps from cyclopentanone, was feasible. The substrate was prepared in the same manner as the cyclohexanone derivative. *N,N*-Dimethylhydrazine was condensed with cyclopentanone followed by deprotonation and alkylation with 2-bromobenzyl bromide. Wittig reaction

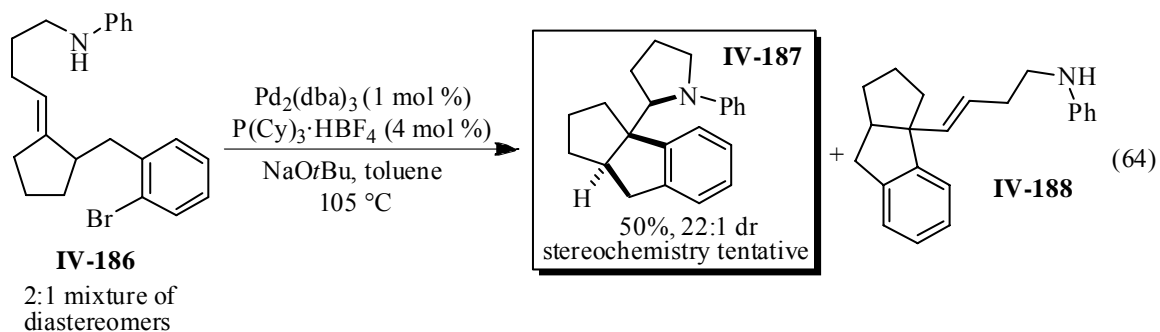
of **IV-182** with the ylide generated from reaction of 4-ethoxy-4-oxobutyl triphenylphosphonium bromide with potassium *tert*-butoxide provided **IV-183** as a 2:1 mixture of diastereomers. The ester was then treated with the anion of aniline to provide **IV-185**, which was then reduced to **IV-186** with lithium aluminum hydride. Alternatively, reduction of ester **IV-183** provides alcohol **IV-184**, which was used for the carboetherification reaction. The stereochemistry was assigned by analogy to **IV-179** which was prepared using the same methods.

Scheme 72. Synthesis of **IV-184** and **IV-186**



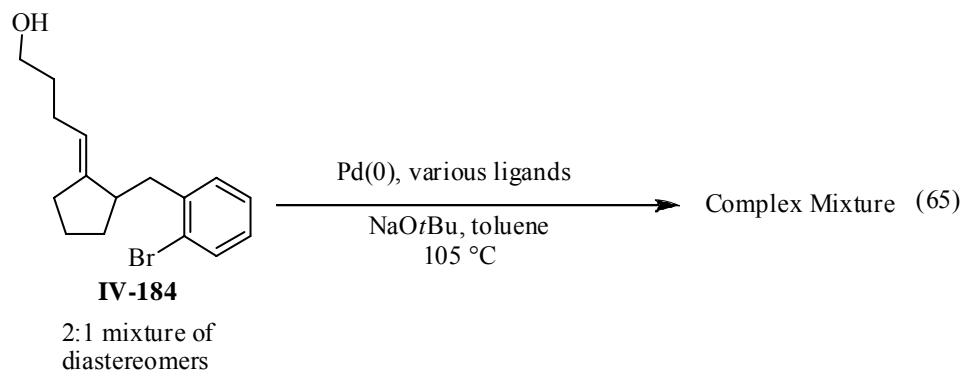
Treatment of amine **IV-186** with typical carboamination conditions provides pyrrolidine **IV-167** in 50% yield and excellent diastereoselectivity. It is probable the

yield of the carboamination reaction of **IV-186** to **IV-187** is higher (eq 64). The inseparable mixture of olefin diastereomers complicates the analysis of the reaction. The geometry of the olefin was assigned by analogy to the six-membered ring derivative on which a NOESY-2D was obtained. It appears that one olefin isomer (**IV-186**), which is assumed to be the *E*-olefin reacts to provide pyrrolidine **IV-187**. The other olefin isomer also reacts, as evidenced by the lack of starting material remaining. Since the stereoselectivity of the reaction is 22:1 dr, it is reasonable to assume that *Z*-olefin is not undergoing the carboamination reaction under these reaction conditions and actually provides the Heck product, which was also isolated. This example nicely illustrates a potential solution in complex molecule synthesis. In a situation such as this, when one olefin geometry does not undergo the desired transformation in an otherwise stereospecific cyclization, simply changing the catalyst in order to get the desired diastereomer is a very effective solution.



Many attempts to cyclize substrate **IV-184** with catalysts composed of $\text{Pd}_2(\text{dba})_3$ and various ligands led to complex mixtures. Although the carboamination of **IV-186** to

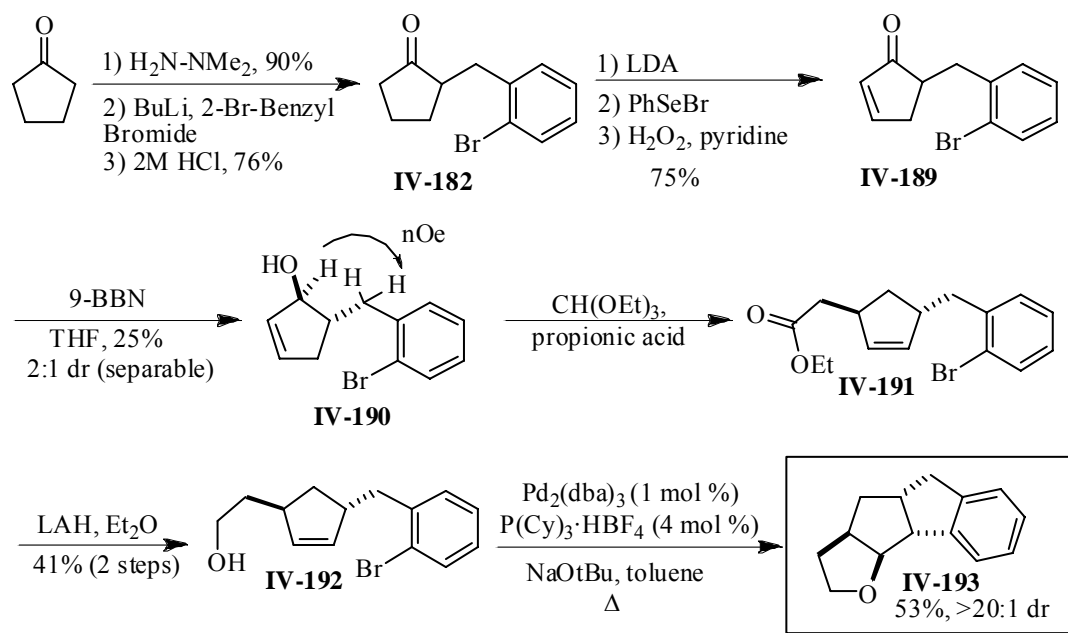
afford **IV-187** was successful, the analogous carboetherification of **IV-184** could not be accomplished (eq 65).



Cyclic olefin-containing substrates (**IV-192**) were also examined in the intramolecular carboetherification reaction. Compound **IV-192** was prepared in 5 steps via condensation of *N,N*-dimethylhydrazine with cyclopentanone, followed by deprotonation with butyllithium and alkylation with 2-bromobenzyl bromide. Hydrolysis provided ketone **IV-182**, which was treated with LDA followed by PhSeBr.⁴² Oxidation and α -elimination of the alkyl selenide provided enone **IV-189**. Reduction of **IV-189** with 9-BBN provided the allylic alcohol (to **IV-190**) and the stereochemistry of the major diastereomer was confirmed by a NOESY-2D experiment of the major diastereomer as shown in Scheme 73. The major diastereomer was converted to ester **IV-191** via a Johnson ortho ester Claisen reaction. Reduction with lithium aluminum hydride afforded substrate **IV-192**. The carboetherification reaction was conducted under standard conditions to yield tetrahydrofuran **IV-193** in good yield and excellent diastereoselectivity in six steps from cyclopentanone. This example illustrates that

reactions can proceed via anti-oxypalladation if a syn-oxypalladation mechanistic manifold cannot be accessed due to substrate geometry.

Scheme 73. Synthesis and Carboetherification of IV-191 to IV-192



Conclusion

In conclusion, we have demonstrated the feasibility of a new strategy for the stereoselective construction of products bearing two attached rings via Pd-catalyzed carboetherification and carboamination reactions. Depending on the structure of the catalyst and the substrate, selectivity for either syn-addition or anti-addition is observed. The products of syn-addition appear to derive from unprecedented transannular alkene insertions of unusual 11-membered Pd(Ar)(YR) intermediates. In contrast, the products of anti-addition are consistent with reaction via a different mechanistic pathway that may involve Wacker-type anti-heteropalladation of the alkene. These studies represent the

first examples of phosphine ligand control of syn-insertion versus anti-addition pathways in catalytic reactions involving olefin oxypalladation, which allows for stereoselective construction of either of two possible product diastereomers from a given alcohol substrate. We have also demonstrated that it is possible to reverse the diastereoselectivity of the Pd-catalyzed carboamination reaction by replacing the group on nitrogen with a Boc-protecting group. We have also demonstrated the utility of the intramolecular Pd-catalyzed carboamination and carboetherification reaction for the synthesis of compound **IV-187** and **IV-193** via a five and six step route, respectively from cyclopentanone.

Throughout the course of our studies of the Pd-catalyzed carboetherification and carboamination reaction, we have learned many things. There are several complicated factors and features relevant to these systems and we have in our work simply touched the surface. In effect, this study though initially unplanned has allowed us to better understand the factors that control syn versus anti-oxypalladation and aminopalladation. We have learned that various factors affect these systems, including but not limited to: heteroatom (oxygen versus nitrogen), acidity, nucleophilicity, protecting group, and substitution or sterics.

This study has also proven that the catalyst and the phosphine ligand in particular greatly affect the course and consequently the mechanism of the reaction. In this realm, the electronics, sterics, bite angle, cone angle, and coordination number all play a role in determining how the reaction proceeds and ultimately how it ends.

Experimental

General Considerations. All reactions were carried out under an argon or nitrogen atmosphere in oven- or flame-dried glassware. All reagents were purchased from commercial sources and were used as obtained unless otherwise noted. Tris(dibenzylideneacetone)dipalladium (0) and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. 3-(2-bromophenyl)propanal (**IV-44**)⁴³ and *E*-7-(2-bromophenyl)hept-4-enoic acid ethyl ester (**IV-47**)⁴⁴ were prepared according to literature procedures. Toluene, diethyl ether, THF, and methylene chloride were purified using a Glass Contour solvent purification system. Aniline was purified by distillation from calcium hydride under nitrogen. The regiochemistry of the heterocyclic products was assigned on the basis of ¹H NMR 2-D COSY experiments; stereochemistry was assigned on the basis of X-ray crystallography and/or ¹H NMR nOe experiments. Ratios of diastereomers were determined by ¹H NMR and/or capillary GC analysis. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ¹H NMR, and either capillary GC or combustion analysis. The yields reported in the supporting information describe the result of a single experiment, whereas the optimized yields reported in Tables 16-21 and 23 and Schemes 50, 51 and 61, and eq 43,45, 46,47 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Tables 16-21 and 23 and Schemes 50, 51 and 61, and eq 43,45, 46,47.

Synthesis of Substrates

Synthesis of Substrate Precursors IV-46 and IV-47

The substrates employed in these studies were generated from *E*-7-(2-bromophenyl)hept-4-enoic acid ethyl ester (**IV-47**) or *Z*-7-(2-bromophenyl)hept-4-enoic acid ethyl ester (**IV-46**), which served as common intermediates for the generation of all substrates employed in the intramolecular carboetherification and carboamination reactions. The esters were prepared from 3-(2-bromophenyl)propanal (**IV-44**),⁴³ which was synthesized via Heck-coupling of allyl alcohol with 1-bromo-2-iodobenzene. Aldehyde **IV-44** was elaborated to *E*-ester **IV-47** via vinyl Grignard addition followed by orthoester Claisen rearrangement,⁴⁴ and the *Z*-ester **IV-46** was obtained via Wittig olefination of **IV-44**.

***Z*-7-(2-Bromophenyl)hept-4-enoic acid ethyl ester (IV-46).** A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with 4-(ethoxycarbonyl)butyltriphenylphosphonium bromide⁴⁵ (17.72 g, 38.77 mmol) and THF (180 mL). The flask was cooled to $-78\text{ }^{\circ}\text{C}$, solid potassium *t*-butoxide (4.34 g, 38.77 mmol) was added, and the resulting yellow solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 45 minutes. A solution of 3-(*o*-bromophenyl)propanal⁴⁴ (7.12 g, 33.43 mmol) in THF (20 mL) was then added and the reaction mixture was stirred for an additional 45 minutes at $-78\text{ }^{\circ}\text{C}$ then warmed to room temperature over several hours. After the starting aldehyde had been consumed as judged by TLC analysis (ca. 8 h) the reaction mixture was quenched with water and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated

in vacuo. The crude product was purified by flash column chromatography using 5% ethyl acetate/hexanes as the eluant to afford 8.46 g (81%) of the title compound as a colorless oil. The alkene configuration was judged to be >95% *Z* by NMR and GC analysis. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, *J* = 8.4 Hz, 1 H), 7.25–7.20 (m, 2 H), 7.07–7.03 (m, 1 H), 5.52–5.35 (m, 2 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 2.80–2.76 (m, 2 H), 2.41–2.22 (m, 6 H), 1.25 (t, *J* = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) d 173.4, 141.2, 133.0, 130.8, 129.8, 128.9, 127.8, 127.5, 124.6, 60.5, 36.3, 34.5, 27.7, 23.0, 14.5; IR (film) 2978, 1734 cm⁻¹; MS (EI) 310.0562 (310.0568 calcd for C₁₅H₁₉BrO₂).

Synthesis of Substrates Bearing Tethered Alcohols (Scheme 44 and Scheme 46).

Esters **IV-46** and **IV-47** were converted to substrates bearing tethered alcohol groups as shown in Schemes 44 and Scheme 46. Treatment of **IV-47** and **IV-46** with LiAlH₄ provided primary alcohols **IV-48** and **IV-56**. Tertiary alcohols **IV-50** and **IV-58** were prepared by treatment of **IV-44** and **IV-47** with methylmagnesium bromide. Secondary alcohols **IV-49** and **IV-57** were generated by oxidation of **IV-48** and **IV-56** with SO₃•pyr/dmsO followed by treatment of the resulting aldehydes with phenylmagnesium bromide. Experimental procedures and characterization data are given below.

***E*-7-(2-Bromophenyl)hept-4-en-1-ol (IV-48)**. A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with *E*-7-(2-bromophenyl)hept-4-enoic acid ethyl ester (1.04 g, 3.34 mmol) and diethyl ether (15 mL). The solution was cooled to 0 °C, a solution of LiAlH₄ (6.6 mL, 6.6 mmol, 1 M in diethyl ether) was added dropwise, and the reaction mixture was warmed to room temperature and stirred for 8 h. The reaction mixture was then cooled to 0 °C and water

(1 mL) was added dropwise followed by 10 M NaOH (2 mL) and additional water (3 mL). The resulting mixture was decanted, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography using 10% ethyl acetate/hexanes as the eluant to afford 620 mg (69%) of the title compound as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.52 (d, $J = 8.0$ Hz, 1 H), 7.24–7.18 (m, 2 H), 7.07–7.03 (m, 1 H), 5.55–5.41 (m, 2 H), 3.62 (app. q, $J = 6.0$ Hz, 2 H), 2.81–2.77 (m, 2 H), 2.34–2.28 (m, 2 H), 2.11–2.05 (m, 2 H), 1.65–1.57 (m, 2 H), 1.26–1.22 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.4, 133.0, 130.6, 130.7, 129.9, 127.7, 127.5, 124.7, 62.7, 36.4, 32.9, 32.5, 29.0; IR (film) 3341, 2931, 1566 cm^{-1} . Anal calcd for $\text{C}_{13}\text{H}_{17}\text{BrO}$: C, 58.01; H, 6.37. Found: C, 58.21; H, 6.37.

Z-7-(2-Bromophenyl)hept-4-en-1-ol (IV-56). Treatment of Z-7-(2-bromophenyl)hept-4-enoic acid ethyl ester (3.81 g, 12.25 mmol) with LiAlH_4 (24 mL, 24 mmol, 1 M in diethyl ether) using a procedure analogous to that described above for the synthesis of **IV-48** afforded 2.64 g (80%) of the title compound as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.53 (d, $J = 8.0$ Hz, 1 H), 7.25–7.20 (m, 2 H), 7.07–7.03 (m, 1 H), 5.51–5.39 (m, 2 H), 3.58 (t, $J = 6.4$ Hz, 2 H), 2.80–2.76 (m, 2 H), 2.41–2.35 (m, 2 H), 2.11–2.05 (m, 2 H), 1.60–1.52 (m, 2 H), 1.24 (s, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.3, 132.9, 130.8, 130.3, 129.1, 127.7, 127.5, 124.6, 62.6, 36.3, 32.6, 27.7, 23.7; IR (film) 3336, 3005 cm^{-1} . Anal calcd for $\text{C}_{13}\text{H}_{17}\text{BrO}$: C, 58.01; H, 6.37. Found: C, 58.41; H, 6.48.

E-8-(2-Bromophenyl)-2-methyloct-5-en-2-ol (IV-50). A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with E-7-(2-bromophenyl)hept-4-enoic acid ethyl ester (0.723 g, 2.32 mmol) and diethyl ether (8

mL). The reaction mixture was cooled to 0 °C and methylmagnesium bromide (2.3 mL, 6.97 mmol, 3 M in THF) was added slowly. The resulting mixture was warmed to room temperature and stirred for 8 h. The reaction mixture was then quenched with aqueous NH₄Cl and transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 x 100 mL) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography using 5% ethyl acetate/hexanes as the eluant to afford 525 mg (76%) of the title compound as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, *J* = 8.0 Hz, 1 H), 7.24–7.18 (m, 2 H), 7.07–7.02 (m, 1 H), 5.56–5.44 (m, 2 H), 2.78 (t, *J* = 7.6 Hz, 2 H), 2.33–2.28 (m, 2 H), 2.12–2.05 (m, 2 H), 1.55–1.51 (m, 2 H), 1.31 (s, 1 H), 1.22 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 141.4, 132.9, 131.4, 130.6, 129.3, 127.7, 127.5, 124.7, 71.2, 43.6, 36.4, 32.9, 29.5, 27.8; IR (film) 3380, 2966, 1566 cm⁻¹. Anal calcd for C₁₅H₂₁BrO: C, 60.61; H, 7.12. Found: C, 60.78; H, 7.21.

Z-8-(2-Bromophenyl)-2-methyloct-5-en-2-ol (IV-58). Treatment of 1.22 g (3.92 mmol) of Z-7-(2-bromophenyl)hept-4-enoic acid ethyl ester with methylmagnesium bromide (3.9 mL, 11.8 mmol, 3 M in Et₂O) using a procedure analogous to that described above for the synthesis of **IV-50** afforded 827 mg (71%) of the title compound as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.52 (d, *J* = 8.0 Hz, 1 H), 7.24–7.18 (m, 2 H), 7.07–7.02 (m, 1 H), 5.48–5.39 (m, 2 H), 2.79 (t, *J* = 7.6 Hz, 2 H), 2.42–2.36 (m, 2 H), 2.08–2.02 (m, 2 H), 1.43 (s, br, 1 H), 1.40–1.36 (m, 2 H), 1.18 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 141.4, 133.0, 131.0, 130.9, 128.6, 127.8, 127.5, 124.7, 71.1, 43.7, 36.4, 29.4, 27.7, 22.5; IR (film) 3388, 2966, 1566 cm⁻¹. Anal calcd for C₁₅H₂₁BrO: C, 60.61; H, 7.12. Found: C, 60.80; H, 7.10.

***E*-7-(2-Bromophenyl)-1-phenylhept-4-en-1-ol (IV-49).** A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with alcohol **IV-48** (2.19 g, 8.17 mmol), methylene chloride (20 mL), and triethylamine (5.1 mL, 36.8 mmol). The flask was cooled to 0 °C and DMSO (23.2 mL, 327 mmol) was added to the reaction mixture followed by SO₃·pyridine (4.03 g, 25.3 mmol). The resulting suspension was stirred at 0 °C for 1 h then warmed to room temperature and stirred for 7 h. The reaction mixture was quenched with aqueous NaHCO₃ and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5% ethyl acetate/hexanes as the eluant to provide 1.63 g (74%) of *E*-7-(2-Bromophenyl)-1-phenylhept-4-en-1-al as a yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 9.75 (s, 1 H), 7.54–7.50 (m, 1 H), 7.25–7.16 (m, 2 H), 7.08–7.02 (m, 1 H), 5.58–5.38 (m, 2 H), 2.81–2.75 (m, 2 H), 2.51–2.46 (m, 2 H), 2.36–2.27 (m, 4 H).

A flame-dried flask equipped with a magnetic stirbar was charged with phenylmagnesium bromide (12 mL, 12.0 mmol, 1 M in THF) and cooled to 0 °C. A solution of *E*-7-(2-bromophenyl)-1-phenylhept-4-en-1-al (965 mg, 3.61 mmol) in THF (10 mL) was added, and the reaction mixture was warmed to room temperature and stirred for 8 h. The reaction mixture was quenched with aqueous NH₄Cl, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5% ethyl acetate/hexanes as the eluant to afford 1.19 g (96%)

of the title compound as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.52 (d, $J = 6.8$ Hz, 1 H), 7.37–7.32 (m, 4 H), 7.29–7.27 (m, 1 H), 7.24–7.18 (m, 2 H), 7.06–7.02 (m, 1 H), 5.54–5.43 (m, 2 H), 4.65 (dd, $J = 4.4, 6.0$ Hz, 1 H), 2.80–2.77 (m, 2 H), 2.34–2.29 (m, 2 H), 2.14–2.02 (m, 2 H), 1.89–1.82 (m, 1 H), 1.79–1.72 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.8, 141.3, 132.9, 130.6, 130.5, 129.9, 128.6, 127.7, 127.6, 127.4, 126.1, 124.6, 74.1, 38.8, 36.3, 32.9, 29.0; IR (film) 3365 cm^{-1} . Anal calcd for $\text{C}_{19}\text{H}_{21}\text{BrO}$: C, 66.09; H, 6.13. Found: C, 66.42; H, 6.15.

Z-7-(2-Bromophenyl)-1-phenylhept-4-en-1-ol (IV-57). Alcohol **IV-56** (2.64 g, 9.85 mmol) was converted to *Z*-7-(2-Bromophenyl)-1-phenylhept-4-en-1-ol (2.23 g, 85% yield, colorless oil) in a manner analogous to that described above for the synthesis of *E*-7-(2-Bromophenyl)-1-phenylhept-4-en-1-ol. ^1H NMR (400 MHz, CDCl_3) δ 9.69 (s, 1 H), 7.52 (d, $J = 7.6$ Hz, 1 H), 7.27–7.19 (m, 2 H) 7.07–7.03 (m, 1 H), 5.41–5.34 (m, 2 H), 2.80–2.76 (m, 2 H), 2.39–2.25 (m, 6 H).

Z-7-(2-Bromophenyl)-1-phenylhept-4-en-1-ol (1.63 g, 6.06 mmol) was converted to the title compound (1.46 g, 70% yield) in a manner analogous to that described above for the synthesis of **IV-49**. ^1H NMR (400 MHz, CDCl_3) δ 7.46–7.44 (m, 1 H), 7.30–7.26 (m, 2 H), 7.25–7.17 (m, 3 H) 7.15–7.10 (m, 2 H), 6.99–6.95 (m, 1 H), 5.45–5.34 (m, 2 H), 4.57–4.53 (m, 1 H), 2.72–2.67 (m, 2 H), 2.31–2.26 (m, 2 H), 2.06–1.96 (m, 2 H), 1.78–1.77 (m, 1 H), 1.76–1.67 (m, 1 H), 1.64–1.55 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.8, 141.3, 132.9, 130.8, 130.3, 129.2, 128.6, 127.8, 127.7, 127.5, 126.1, 124.6, 74.3, 39.0, 36.4, 27.7, 23.9; IR (film) 3369, 2930, 1470 cm^{-1} . Anal calcd for $\text{C}_{19}\text{H}_{21}\text{BrO}$: C, 66.09; H, 6.13. Found: C, 66.39; H, 6.21.

Synthesis of Substrates Bearing Amine Nucleophiles

As shown in Schemes 45 and Scheme 47, unbranched aniline derivatives **IV-52** and **IV-60** were generated via amidation of **IV-47** and **IV-46** followed by reduction with LiAlH₄. Branched substrates **IV-55** and **IV-63** were prepared via conversion of esters **IV-47** and **IV-46** to the corresponding Weinreb Amides followed by addition of phenylmagnesium bromide to generate phenyl ketone derivatives. Conversion of these intermediates to *N*-aryl imines followed by reduction with LiAlH₄ generated **IV-55** and **IV-63**. Experimental procedures and characterization data are given below.

***E*-[7-(2-Bromophenyl)hept-4-enyl]aniline (IV-52)**. A flame-dried flask was cooled under a stream of nitrogen and charged with aniline (0.6 mL, 6.52 mmol) and tetrahydrofuran (6 mL). The mixture was cooled to 0°C, a solution of methylmagnesium bromide (2.2 mL, 6.6 mmol, 3 M in diethyl ether) was added dropwise, and the reaction mixture was warmed to room temperature and stirred for 12 h. A solution of *E*-7-(2-bromophenyl)hept-4-enoic acid ethyl ester (1.03 g, 3.31 mmol) in tetrahydrofuran (6 mL) was added to the reaction mixture, and the resulting solution was stirred at room temperature for 12 h. The reaction was quenched with water, the layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 200 mL). The combined organic extracts were washed sequentially with 2M HCl (2 x 100 mL) aqueous NaHCO₃, and brine, and were then dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5%→10% ethyl acetate/hexanes as the eluant to afford 710 mg (60%) of *E*-7-(2-bromophenyl)hept-4-enoic acid phenyl amide as a gray solid, m.p. 80–85 °C. ¹H NMR (400 MHz, CDCl₃) δ

7.58–7.50 (m, 3 H), 7.44–7.31 (m, 2 H), 7.22–7.18 (m, 3 H), 7.06–7.00 (m, 1 H), 5.64–5.55 (m, 2 H), 2.79 (t, $J = 7.2$ Hz, 2 H), 2.48–2.42 (m, 4 H), 2.36–2.32 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 141.2, 138.1, 132.8, 130.8, 130.6, 129.3, 129.1, 127.7, 127.5, 124.6, 124.4, 120.2, 37.5, 36.2, 32.8, 28.6; IR (film) 3296, 1652 cm^{-1} . Anal calcd for $\text{C}_{19}\text{H}_{20}\text{BrNO}$: C, 63.70; H, 5.63; N, 3.91. Found: C, 63.49; H, 5.67; N, 3.85.

A flame-dried flask was cooled under nitrogen and charged with *E*-7-(2-bromophenyl)hept-4-enoic acid phenyl amide (690 mg, 1.93 mmol) and diethyl ether (10 mL). The solution was cooled to 0 °C and LiAlH_4 (5.78 mL, 5.78 mmol, 1 M in diethyl ether) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 10 h, then was cooled to 0 °C and water (1 mL) was added dropwise followed by 10 M NaOH (2 mL) and additional water (3 mL). The resulting mixture was decanted, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5%→10% ethyl acetate/hexanes as the eluant to afford 523 mg (70%) of the title compound as an orange oil. ^1H NMR (400 MHz, CDCl_3) δ 7.52 (d, $J = 6.0$ Hz, 1 H), 7.24–7.16 (m, 4 H), 7.06–7.02 (m, 1 H), 6.70 (t, $J = 7.2$ Hz, 1 H), 6.61 (d, $J = 7.6$ Hz, 2 H), 5.56–5.42 (m, 2 H), 3.84 (s, br, 1 H), 3.09 (t, $J = 7.2$ Hz, 2 H), 2.82–2.78 (m, 2 H), 2.35–2.29 (m, 2 H), 2.13–2.08 (m, 2 H), 1.70–1.65 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.6, 141.4, 132.9, 130.6, 130.5, 130.0, 129.4, 127.7, 127.5, 124.7, 117.4, 113.0, 43.6, 36.4, 32.9, 30.2, 29.3; IR (film) 3411, 2928, 1603 cm^{-1} . Anal calcd for $\text{C}_{19}\text{H}_{22}\text{BrN}$: C, 66.28; H, 6.44; N, 4.07. Found: C, 66.53; H, 6.40; N, 4.12.

Z-[7-(2-Bromophenyl)hept-4-enyl]aniline (IV-60). *Z*-7-(2-bromophenyl)hept-4-enoic acid ethyl ester (941 mg, 3.02 mmol) was converted to *Z*-7-(2-bromophenyl)hept-4-enoic acid phenyl amide (755 mg, 70% yield, colorless oil) in a manner analogous to that described above for the synthesis of *E*-7-(2-bromophenyl)hept-4-enoic acid phenyl amide. ¹H NMR (400 MHz, CDCl₃) δ 7.54–7.48 (m, 3 H), 7.32–7.18 (m, 4 H), 7.10–7.03 (m, 2 H), 5.56–5.41 (m, 2 H), 2.79 (t, *J* = 8.0 Hz, 2 H), 2.44–2.36 (m, 4 H), 2.23–2.19 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 170.9, 141.2, 138.1, 132.9, 131.0, 130.2, 129.2, 128.9, 127.8, 127.5, 124.6, 124.4, 120.0, 37.7, 36.2, 27.6, 23.5; IR (film) 3302, 1651 cm⁻¹.

Z-7-(2-bromophenyl)hept-4-enoic acid phenyl amide (585 mg, 1.63 mmol) was converted to the title compound (498 mg, 89% yield) in a manner analogous to that described above for the synthesis of **IV-52**. ¹H NMR (500 MHz, CDCl₃) δ 7.52 (d, *J* = 8.0 Hz, 1 H), 7.25–7.15 (m, 4 H), 7.06–7.03 (m, 1 H), 6.70–6.66 (m, 1 H), 6.58 (d, *J* = 8.0 Hz, 2 H), 5.51–5.40 (m, 2 H), 3.56 (s, br, 1 H), 3.07–3.05 (m, 2 H), 2.78 (t, *J* = 6.4 Hz, 2 H), 2.40–2.35 (m, 2 H), 2.12–2.07 (m, 2 H), 1.61–1.55 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 148.6, 141.3, 133.0, 130.8, 130.2, 129.4, 129.2, 127.8, 127.5, 124.6, 117.3, 112.9, 43.7, 36.4, 29.6, 27.8, 25.0; IR (film) 3409, 2928, 1601 cm⁻¹. Anal calcd for C₁₉H₂₂BrN: C, 66.28; H, 6.44; N, 4.07. Found: C, 66.46; H, 6.62; N, 4.07.

***E*-[7-(2-Bromophenyl)-1-phenylhept-4-enyl]aniline (IV-55).** A flame-dried flask was cooled under a stream of nitrogen and charged with *N,O*-dimethylhydroxylamine hydrochloride (2.3 g, 23.6 mmol) and toluene (30 mL). The mixture was cooled to 0 °C, and a solution of trimethylaluminum (11.8 mL, 23.6 mmol, 2 M in toluene) was added dropwise. The resulting mixture was stirred at 0 °C for 10 min, then a solution of ester

IV-47 (2.94 g, 9.45 mmol) in toluene (16 mL) was added to the reaction mixture *via* cannula. The resulting solution was allowed to slowly warm to room temperature over 10 h with stirring. The reaction mixture was then cooled to 0 °C and 1M HCl was added dropwise. The resulting mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with methylene chloride (3 x 400 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 20% ethyl acetate/hexanes as the eluant to provide 1.88g (61%) of *E*-7-(2-bromophenyl)hept-4-enoic acid (methoxy)methylamide as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.53–7.50 (m, 1 H), 7.24–7.17 (m, 2 H), 7.06–7.02 (m, 1 H), 5.58–5.44 (m, 2 H), 3.67 (s, 3 H), 3.18 (s, 3 H), 2.80–2.76 (m, 2 H), 2.49–2.45 (m, 2 H), 2.35–2.27 (m, 4 H).

A flame-dried flask was cooled under a stream of nitrogen and charged with *E*-7-(2-bromophenyl)-hept-4-enoic acid (methoxy)methylamide (1.88 g, 5.76 mmol) and THF (10 mL). The mixture was cooled to 0 °C, a solution of phenylmagnesium bromide (17.3 mL, 17.3 mmol, 1 M in THF) was added dropwise, and the reaction mixture was warmed to room temperature with stirring over 8 h. The reaction mixture was then cooled to 0 °C, water (5 mL) was added dropwise, and the reaction mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluant to provide 1.34 g (69%) of *E*-7-(2-bromophenyl)-1-phenylhept-4-en-1-one as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.97–7.95 (m, 2 H), 7.61–7.43 (m, 4 H), 7.21–7.19 (m, 2 H) 7.05–7.01 (m, 1 H), 5.60–5.48 (m, 2 H), 3.04–3.00 (m, 2 H), 2.80–2.76 (m, 2 H), 2.46–2.41 (m, 2 H), 2.33–2.28 (m, 2 H).

A flame-dried flask equipped with Dean-Stark apparatus and reflux condenser was cooled under a stream of nitrogen and charged with *E*-7-(2-bromophenyl)-1-phenylhept-4-en-1-one (1.34 g, 3.90 mmol), aniline (397 mg, 389 μL , 4.27 mmol), benzene (20 mL), and trifluoroacetic acid (29.0 μL , 0.390 mmol). The mixture was heated to reflux under nitrogen for 48h with azeotropic removal of water. The reaction mixture was then cooled to room temperature, concentrated *in vacuo*, and diluted with diethyl ether. The resulting solution was cooled to 0 °C and a solution of lithium aluminum hydride (11.7 mL, 11.7 mmol, 1 M in ether) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 8 h. The reaction mixture was then cooled to 0°C, and H_2O (2 mL) followed by 10 M NaOH (3 mL) and additional water. The resulting suspension was decanted, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluant to afford 958 mg (59%) of the title compound as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.53–7.51 (m, 1 H), 7.32–7.28 (m, 4 H), 7.24–7.20 (m, 1 H), 7.19–7.17 (m, 2 H), 7.10–7.02 (m, 3 H), 6.63 (t, $J = 7.6$ Hz, 1 H), 6.50 (d, $J = 7.6$ Hz, 2 H), 5.53–5.42 (m, 2 H), 4.30 (t, $J = 6.8$ Hz, 1 H), 4.06 (s, 1 H), 2.80–2.76 (m, 2 H), 2.33–2.28 (m, 2 H), 2.10–2.05 (m, 2 H), 1.89–1.81 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.6, 144.2, 141.3, 133.0, 130.6, 130.32, 130.28, 129.3, 128.7, 127.7, 127.5, 127.1, 126.6, 124.7, 117.4, 113.4, 57.8, 38.6, 36.4, 32.9, 29.5; IR (film) 3412, 2929, 1600 cm^{-1} . Anal calcd for $\text{C}_{25}\text{H}_{26}\text{BrN}$: C, 71.43; H, 6.23; N, 3.33. Found: 71.44; H, 6.30; N, 3.35.

Z-[7-(2-Bromophenyl)-1-phenylhept-4-enyl]aniline (IV-63). Z-7-(2-

bromophenyl)hept-4-enoic acid ethyl ester (1.44 g, 4.63 mmol) was converted to Z-7-(2-bromophenyl)hept-4-enoic acid (methoxy)methylamide (1.02 g, 68% yield, colorless oil) in a manner analogous to that described above for the synthesis of E-7-(2-bromophenyl)hept-4-enoic acid (methoxy)methylamide. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, *J* = 7.6 Hz, 1 H), 7.25–7.16 (m, 2 H), 7.06–7.02 (m, 1 H), 5.51–5.40 (m, 2 H), 3.66 (s, 3 H), 3.17 (s, 3 H), 2.80–2.76 (m, 2 H), 2.42–2.39 (m, 3 H), 2.37–2.25 (m, 3 H).

Z-7-(2-bromophenyl)hept-4-enoic acid (methoxy)methylamide (1.02 g, 3.13 mmol) was converted to Z-7-(2-bromophenyl)-1-phenylhept-4-en-1-one (760 mg, 71% yield, colorless oil) in a manner analogous to that described above for the synthesis of E-7-(2-bromophenyl)-1-phenylhept-4-en-1-one. ¹H NMR (400 MHz, CDCl₃) δ 7.94–7.91 (m, 2 H), 7.58–7.44 (m, 4 H), 7.21–7.19 (m, 2 H) 7.04–7.00 (m, 1 H), 5.53–5.43 (m, 2 H), 2.91–2.87 (m, 2 H), 2.81–2.77 (m, 2 H), 2.45–2.38 (m, 4 H).

Z-7-(2-bromophenyl)-1-phenylhept-4-en-1-one (750 mg, 2.19 mmol) was converted to the title compound (531 mg, 58% yield, colorless oil) in a manner analogous to that described above for the synthesis of IV-55. ¹H NMR (500 MHz, CDCl₃) δ 7.48–7.46 (m, 1 H), 7.24–7.20 (m, 4 H), 7.19–7.12 (m, 2 H), 7.07–6.97 (m, 4 H), 6.57 (dt, *J* = 1.0, 7.5 Hz, 1 H), 6.46 (d, *J* = 8.5 Hz, 2 H), 5.45–5.34 (m, 2 H), 4.23 (t, *J* = 6.5 Hz, 1 H), 3.97 (s, 1 H), 2.70–2.66 (m, 2 H), 2.30–2.21 (m, 2 H), 2.05–1.96 (m, 2 H), 1.70–1.63 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 147.5, 144.1, 141.2, 132.9, 130.8, 129.9, 129.4, 129.2, 128.7, 127.8, 127.4, 127.1, 126.5, 124.6, 117.3, 113.4, 57.9, 38.8, 36.3, 27.7, 24.3; IR (film) 3413, 2927 cm⁻¹. Anal calcd for C₂₅H₂₆BrN: C, 71.43; H, 6.23; N, 3.33. Found: C, 71.35; H, 6.21; N, 3.20.

General Procedure for Pd-Catalyzed Cyclization Reactions

A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with Pd₂(dba)₃ (1 mol % complex, 2 mol % palladium), ligand (4 mol %), and NaOtBu (2.0 equiv). The tube was purged with nitrogen and a solution of the alcohol substrate in toluene (2.5 mL/0.5 mmol substrate) was added via cannula. An additional 1.0 mL of toluene was added and the resulting mixture was heated to 105 °C with stirring for 3–8 hours until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature, aqueous NH₄Cl (2 mL) and ethyl acetate (10 mL) were added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography.

(±)-(1*S**,2*R**)-2-Indan-1-yltetrahydrofuran (**IV-65**). The cyclization of **IV-48** (150 mg, 0.56 mmol) following the general procedure using PCy₃•HBF₄ as the ligand afforded 54 mg (52%) of the title compound as a colorless oil. This compound was judged to be a >20:1 mixture of diastereomers by GC analysis. ¹H NMR (400 MHz, CDCl₃) δ 7.51–7.49 (m, 1 H), 7.22–7.19 (m, 1 H), 7.18–7.13 (m, 2 H), 3.98–3.90 (m, 2 H), 3.82–3.77 (m, 1 H), 3.32–3.26 (m, 1 H), 2.98–2.83 (m, 2 H), 2.24–2.15 (m, 1 H), 2.00–1.83 (m, 3 H), 1.81–1.72 (m, 1 H), 1.64–1.54 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 145.2, 144.4, 126.8, 126.3, 125.6, 124.5, 83.1, 68.3, 49.8, 31.8, 29.9, 28.3, 25.8; IR (film) 2952, 2858, 1474, 1457 cm⁻¹. Anal calcd for C₁₃H₁₆O: C, 82.94; H, 8.57. Found: C, 83.07; H, 8.69.

(±)-(1*S,2*R**)-2-Indan-1-yltetrahydrofuran (IV-65).** The cyclization of **IV-56** (190 mg, 0.71 mmol) following the general procedure using (±)-BINAP as the ligand afforded 79 mg (59%) of the title compound as a colorless oil. This compound was judged to be an 18:1 mixture of diastereomers by GC analysis. Spectroscopic data were identical to those given above.

(±)-(1*S,2*S**)-2-Indan-1-yltetrahydrofuran (IV-64).** The cyclization of **IV-56** (132 mg, 0.492 mmol) following the general procedure using [(*p*-MeO)C₆H₄]₃P as ligand afforded 48 mg (57%) of the title compound as a colorless oil. This compound was judged to be an 8:1 mixture of diastereomers by GC analysis. Data are for the major isomer. ¹H NMR (400 MHz, CDCl₃) δ 7.32–7.29 (m, 1 H), 7.23–7.19 (m, 1 H), 7.17–7.15 (m, 2 H), 4.03–3.98 (m, 1 H), 3.91–3.85 (m, 1 H), 3.79–3.74 (m, 1 H), 3.38–3.33 (m, 1 H), 3.02–2.94 (m, 1 H), 2.89–2.81 (m, 1 H), 2.28–2.19 (m, 1 H), 2.08–1.97 (m, 2 H), 1.93–1.85 (m, 2 H), 1.68–1.59 (m, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 145.7, 144.2, 126.9, 126.2, 125.0, 124.7, 81.7, 68.2, 49.8, 31.4, 29.5, 28.3, 26.4; IR (film) 2925 cm⁻¹; Anal calcd for C₁₃H₁₆O: C, 82.94; H, 8.57. Found: C, 82.98; H, 8.25.

(±)-(1*S,2*S**)-2-Indan-1-yltetrahydrofuran (IV-64).** The cyclization of **IV-48** (70 mg, 0.26 mmol) following the general procedure using dpp-benzene as the ligand afforded 28 mg (58%) of the title compound as a colorless oil. This compound was judged to be a 15:1 mixture of diastereomers by GC analysis. Spectroscopic data were identical to those given above.

(±)-(1*S,5*R**)-2,2-Dimethyl-5-indan-1-yltetrahydrofuran (IV-77).** The cyclization of **IV-50** (150 mg, 0.51 mmol) following the general procedure using [(*p*-MeO)C₆H₄]₃P as

ligand afforded 56 mg (51%) of the title compound as a colorless oil. This compound was judged to be a >20:1 mixture of diastereomers by ^1H NMR analysis. ^1H NMR (400 MHz, CDCl_3) δ 7.49–7.47 (m, 1 H), 7.21–7.19 (m, 1 H), 7.18–7.13 (m, 2 H), 4.18–4.13 (m, 1 H), 3.37–3.31 (m, 1 H), 2.97–2.83 (m, 2 H), 2.22–2.14 (m, 1 H), 1.93–1.87 (m, 1 H), 1.85–1.79 (m, 1 H), 1.79–1.61 (m, 3 H), 1.30 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 145.5, 144.5, 126.7, 126.2, 125.6, 124.4, 82.1, 80.9, 50.1, 38.6, 31.9, 29.6, 29.4, 28.4, 27.7; IR (film) 2966, 2865 cm^{-1} . Anal calcd for $\text{C}_{15}\text{H}_{20}\text{O}$: C, 83.28; H, 9.32. Found: C, 83.01; H, 9.32.

(\pm)-(1*S,5*R**)-2,2-Dimethyl-5-indan-1-yltetrahydrofuran (IV-77).** The cyclization of **IV-58** (150 mg, 0.51 mmol) following the general procedure using $\text{PCy}_3\cdot\text{HBF}_4$ as the ligand afforded 86 mg (79%) of the title compound as a colorless oil. This compound was judged to be a 14:1 mixture of diastereomers by ^1H NMR analysis. Spectroscopic data were identical to those given above.

(\pm)-(1*S,5*S**)-2,2-Dimethyl-5-indan-1-yltetrahydrofuran (IV-78).** The cyclization of **IV-58** (200 mg, 0.673 mmol) following the general procedure using $\text{PMe}_3\cdot\text{HBF}_4$ as ligand afforded 110 mg (76%) of the title compound as a colorless oil. This compound was judged to be a 9:1 mixture of diastereomers by ^1H NMR analysis. Data are for the major isomer. ^1H NMR (400 MHz, CDCl_3) δ 7.36 (d, $J = 6.8$ Hz, 1 H), 7.22 (d, $J = 6.8$ Hz, 1 H), 7.19–7.12 (m, 2 H), 4.13–4.08 (m, 1 H), 3.37–3.32 (m, 1 H), 3.01–2.93 (m, 1 H), 2.88–2.80 (m, 1 H), 2.28–2.19 (m, 1 H), 2.05–1.95 (m, 2 H), 1.72–1.61 (m, 3 H), 1.27 (s, 3 H), 1.25 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.2, 145.1, 126.8, 126.0, 125.4,

124.6, 81.0, 80.5, 49.9, 38.9, 31.4, 29.4, 29.2, 28.6, 28.2; IR (film) 2967 cm^{-1} . Anal calcd for $\text{C}_{15}\text{H}_{20}\text{O}$: C, 83.28; H, 9.32. Found: C, 83.03; H, 9.26.

(±)-(1*S,5*S**)-2,2-Dimethyl-5-indan-1-yltetrahydrofuran (IV-78).** The cyclization of **IV-50** (150 mg, 0.51 mmol) following the general procedure using (±)-BINAP as the ligand afforded 35 mg (32%) of the title compound as a colorless oil. This compound was judged to be a 6:1 mixture of diastereomers by ^1H NMR analysis. Spectroscopic data were identical to those given above.

(±)-(1*S,2*R**,5*R**)-2-Indan-1-yl-5-phenyltetrahydrofuran (IV-83).** The cyclization of **IV-49** (150 mg, 0.434 mmol) following the general procedure using $\text{PCy}_3\cdot\text{HBF}_4$ as ligand afforded 46 mg (40%) of the title compound as a yellow oil. This compound was obtained as a 92:5:2:1 mixture of diastereomers **IV-83**: **IV-83b**: **IV-85**: **IV-85b** as judged by ^1H NMR analysis. Data are for the major isomer. ^1H NMR (500 MHz, CDCl_3) δ 7.62–7.59 (m, 1 H), 7.38–7.31 (m, 4 H), 7.25–7.20 (m, 2 H), 7.18–7.14 (m, 2H), 5.14–5.11 (m, 1 H), 4.34–4.28 (m, 1 H), 3.44–3.38 (m, 1 H), 3.00–2.86 (m, 2 H), 2.44–2.38 (m, 1 H), 2.27–2.18 (m, 1 H), 2.12–2.06 (m, 1 H), 1.89–1.74 (m, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 145.5, 144.5, 144.4, 128.5, 127.2, 126.8, 126.4, 125.8, 125.7, 124.5, 83.9, 80.8, 50.2, 35.4, 31.9, 31.0, 28.2; IR (film) 3024, 2958, 1602 cm^{-1} . Anal calcd for $\text{C}_{19}\text{H}_{20}\text{O}$: C, 86.32; H, 7.63. Found: C, 86.45; H, 7.65.

(±)-(1*S,2*R**,5*R**)-2-Indan-1-yl-5-phenyltetrahydrofuran (IV-83).** The cyclization of **IV-57** (122 mg, 0.35 mmol) following the general procedure using (±)-BINAP as the ligand afforded 23 mg (25%) of the title compound as a colorless oil. This compound was

obtained as a 65:29:5:1 mixture of diastereomers **IV-83**: **IV-83b**: **IV-85**: **IV-85b** as judged by ¹H NMR analysis. Spectroscopic data for the major diastereomer (**IV-83**) were identical to those given above.

(±)-(1S*,2S*,5S*)-2-Indan-1-yl-5-phenyltetrahydrofuran (IV-85). The cyclization of **IV-57** (182 mg, 0.529 mmol) following the general procedure using [(*p*-MeO)C₆H₄]₃P as ligand afforded 55 mg (40%) of the title compound as yellow oil. Analysis of the crude reaction mixture by ¹H NMR revealed that a 9:2:2:1 ratio of diastereomers **IV-85**: **IV-85b**: **IV-83**: **IV-83b** was formed. Upon purification the title compound was obtained as a 17:2:1:1 mixture of diastereomers **IV-85**: **IV-85b**: **IV-83**: **IV-83b** as judged by ¹H analysis. Data are for the major diastereomer. ¹H NMR (500 MHz, CDCl₃) δ 7.39–7.37 (m, 1 H), 7.35–7.31 (m, 4 H), 7.26–7.23 (m, 2 H) 7.20–7.17 (m, 2 H), 5.02 (dd, *J* = 2.5, 8.5 Hz, 1 H), 4.39–4.35 (m, 1 H), 3.51–3.47 (m, 1 H), 3.04–2.97 (m, 1 H), 2.92–2.85 (m, 1 H), 2.38–2.31 (m, 1 H), 2.30–2.24 (m, 1 H), 2.15–2.09 (m, 2 H), 1.90–1.75 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 145.3, 144.2, 144.0, 128.5, 127.3, 127.0, 126.2, 125.8, 125.3, 124.7, 82.5, 80.9, 50.0, 36.0, 31.4, 30.3, 28.5; IR (film) 3026, 2942 cm⁻¹. Anal calcd for C₁₉H₂₀O: C, 86.32; H, 7.63. Found: C, 86.12; H, 7.61.

(±)-(1S*,2R*)-N-Phenyl-2-indan-1-ylpyrrolidine (IV-90). The cyclization of **IV-52** (150 mg, 0.436 mmol) following the general procedure using PCy₃•HBF₄ as ligand afforded 85 mg (74%) of the title compound as a colorless oil. This compound was judged to be a >20:1 mixture of diastereomers by ¹H NMR analysis. ¹H NMR (400 MHz, CDCl₃) δ 7.25–7.17 (m, 4 H), 7.15–7.11 (m, 2 H), 6.68–6.63 (m, 3 H), 4.32–4.28 (m, 1 H), 3.85–3.80 (m, 1 H), 3.62–3.57 (m, 1 H), 3.31–3.25 (dd, *J* = 7.6, 16.8 Hz, 1 H), 2.98–

2.91 (m, 1 H), 2.86–2.77 (m, 1 H), 2.09–1.99 (m, 2 H), 1.97–1.81 (m, 3 H), 1.69–1.63 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.0, 145.2, 144.9, 129.2, 126.7, 126.4, 124.7, 124.4, 115.9, 112.6, 60.8, 50.1, 46.8, 31.8, 27.7, 27.3, 24.5; IR (film) 2960, 1597 cm^{-1} . Anal calcd for $\text{C}_{19}\text{H}_{21}\text{N}$: C, 86.65; H, 8.04; N, 5.32. Found: C, 86.42; H, 8.13; N, 5.34.

(\pm)-(1*S,2*S**)-*N*-Phenyl-2-indan-1-ylpyrrolidine (IV-89).** The cyclization of **IV-60** (155 mg, 0.450 mmol) following the general procedure using $\text{PCy}_3\cdot\text{HBF}_4$ as ligand afforded 108 mg (92%) of the title compound as an orange oil. This compound was judged to be a >20:1 mixture of diastereomers by ^1H NMR analysis. ^1H NMR (400 MHz, CDCl_3) δ 7.31–7.27 (m, 2 H), 7.21 (d, $J = 7.6$ Hz, 1 H), 7.17–7.14 (m, 1 H), 7.06 (d, $J = 4.0$ Hz, 2 H), 6.76 (d, $J = 8.0$ Hz, 2 H), (6.73–6.69 (m, 1 H), 4.06–4.04 (m, 1 H), 3.93–3.89 (m, 1 H), 3.44 (dd, $J = 4.0, 8.0$ Hz, 1 H), 3.21–3.15 (m, 1H), 3.11–3.02 (m, 1 H), 2.95–2.88 (m, 1 H), 2.39–2.28 (m, 1 H), 1.96–1.85 (m, 2 H), 1.70–1.61 (m, 2 H), 1.32–1.27 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.7, 145.1, 144.4, 129.4, 126.8, 126.2, 126.0, 124.4, 115.8, 112.6, 63.0, 50.3, 45.6, 32.0, 28.2, 27.6, 24.1; IR (film) 3063, 2942, 1597 cm^{-1} . Anal calcd for $\text{C}_{19}\text{H}_{21}\text{N}$: C, 86.65; H, 8.04; N, 5.32. Found: C, 86.44; H, 8.16; N, 5.31.

(*Z*)-*tert*-butyl 7-(2-bromophenyl)hept-4-enylcarbamate (IV-99).

A flame-dried flask was charged with ammonium chloride (1.53 g, 28.54 mmol), and toluene (29 mL) and cooled to 0 °C and a solution of AlMe_3 in toluene (14.3 mL, 28.54 mmol, 2 M in toluene) was added dropwise. The reaction was stirred at 0 °C then warmed to room temperature and stirred 0.5 h. Ester **IV-46** (3.55 g, 11.41 mmol) dissolved in 10 mL of toluene was added and the reaction mixture was heated to 50 °C

for 12 h. The reaction mixture was cooled to room temperature and 1 M HCl was added slowly until bubbling ceased. The organic product was extracted with ethyl acetate (3 X 150 mL) and then washed with saturated sodium chloride, followed by drying over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography to yield 2.72 g (84%) of (Z)-7-(2-bromophenyl)hept-4-enamide as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.56–7.52 (m, 1 H), 7.28–7.19 (m, 2 H), 7.07–7.04 (m, 1 H), 5.54–5.49 (m, 1 H), 5.43–5.38 (m, 1 H), 5.33 (broad s, 2 H), 2.79 (t, *J* = 7.0 Hz, 2 H), 2.40 (q, *J* = 7.0 Hz, 2 H), 2.31 (q, *J* = 7.5 Hz, 2 H), 2.12 (t, *J* = 8.0 Hz, 2 H).

A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and was charged with (Z)-7-(2-bromophenyl)hept-4-enamide (2.72 g, 9.65 mmol) and diethyl ether (20 mL). The reaction mixture was cooled to 0 °C, and a solution of LiAlH₄ (25 mL, 25 mmol, 1 M in diethyl ether) was added dropwise, and the reaction mixture was warmed to room temperature and stirred for 8 h. The reaction mixture was then cooled to 0 °C and water (1 mL) was added dropwise followed by 10 M NaOH (2 mL) and additional water (3 mL). The resulting mixture was decanted, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to provide 1.54 g (60%) of the crude product ((Z)-7-(2-bromophenyl)hept-4-en-1-amine) which was used without further purification. ¹H NMR (400 MHz, CDCl₃) 7.53 (d, *J* = 8 Hz, 1 H), 7.25–7.19 (m, 2 H), 7.08–7.03 (m, 1 H), 5.48–5.37 (m, 2 H), 2.78 (t, *J* = 7.6 Hz, 2 H), 2.64 (t, *J* = 7.6 Hz, 2 H), 2.39–2.34 (m, 2 H), 2.02 (q, *J* = 7.2 Hz, 2 H), 1.51–1.28 (m, 4 H).

A flask equipped with a magnetic stirbar was placed under nitrogen and was charged with (Z)-7-(2-bromophenyl)hept-4-en-1-amine (1.54 g, 5.75 mmol) and THF (40 mL). Boc₂O

was added (1.26 g, 5.77 mmol) and the reaction was stirred overnight at room temperature. ¹H NMR (300 MHz, CDCl₃) δ 7.51 (d, *J* = 7.5 Hz, 1 H), 7.28–7.18 (m, 2 H), 7.08–7.01 (m, 1 H), 5.50–5.33 (m, 2 H), 4.49 (broad s, 1 H), 3.08–3.02 (m, 2 H), 2.77 (t, *J* = 7.2 Hz, 2 H), 2.35 (q, *J* = 7.5 Hz, 2 H), 2.00 (q, *J* = 6.9 Hz, 2 H), 1.50–1.37 (m, 11 H); ¹³C NMR (75 MHz, CDCl₃) δ 156.1, 141.3, 132.9, 130.8, 130.0, 129.2, 127.8, 127.5, 124.6, 79.2, 40.3, 36.4, 30.1, 28.6, 27.7, 24.6; IR (film) 3356, 2931, 1703 cm⁻¹. MS (ESI) 390.1057 (390.1045 calcd for C₁₈H₂₆BrNO₂, M + Na⁺).

(*R*)-tert-butyl 2-((*S*)-2,3-dihydro-1H-inden-1-yl)pyrrolidine-1-carboxylate (IV-100).

The cyclization of **IV-99** (100 mg, 0.272 mmol) following the general procedure using BINAP as ligand afforded 24 mg (31%) of the title compound as a yellow oil. This compound was judged to be a 1.25:1 mixture of rotamers by ¹H NMR analysis. The diastereoselectivity was not determined at this point. Instead a sample of the crude material was subjected to Boc-cleavage (see below). Data are for the mixture. ¹H NMR (500 MHz, CDCl₃) δ 7.22–7.12 (m, 4 H), 4.29–3.98 (m, 2 H), 3.60–3.34 (m, 2 H), 3.00–2.90 (m, 2 H), 2.88–2.82 (m, 2 H), 2.18–2.04 (m, 1 H), 1.90–1.70 (m, 3 H), 1.46 (s, 4 H), 1.29 (s, 5 H); ¹³C NMR (75 MHz, CDCl₃) δ 155.0, 145.1, 144.7, 126.6, 126.4, 124.7, 124.6, 79.2, 77.4, 60.0, 48.3, 47.0, 31.6, 28.5, 27.7, 23.6; IR (film) 2918, 1692 cm⁻¹. MS (ESI) 310.1780 (310.1783 calcd for C₁₈H₂₅NO₂, M + Na⁺).

(*S*)-tert-butyl 2-((*S*)-2,3-dihydro-1H-inden-1-yl)pyrrolidine-1-carboxylate (IV-101).

The cyclization of **IV-99** (75 mg, 0.204 mmol) following the general procedure using PCy₃•HBF₄ as ligand afforded 30 mg (52%) of the title compound as a yellow oil. This compound was judged to be a 3:1 mixture of rotamers by ¹H NMR analysis. The

diastereoselectivity was not determined at this point. Instead a sample of the crude material was subjected to Boc-cleavage (see below). Data are for the pure mixture. ^1H NMR (400 MHz, CDCl_3) δ 7.21–7.11 (m, 4 H), 4.29–4.00 (m, 0.75 H), 3.88–3.76 (m, 0.25 H), 3.60–3.35 (m, 1 H), 3.16–3.10 (m, 1 H), 3.04–2.92 (m, 1 H), 2.89–2.82 (m, 1 H), 2.26–2.21 (m, 1 H), 1.87–1.80 (m, 3 H), 1.52 (s, 9H), 1.49–1.26 (m, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.2, 145.1, 144.6, 126.9, 126.3, 125.7, 124.59, 124.55, 79.2, 77.4, 61.7, 47.8, 47.4, 47.2, 46.2, 31.9, 28.8, 28.5, 27.8, 26.8, 24.3, 23.6; IR (film) 2927, 1692 cm^{-1} . MS (ESI) 310.1776 (310.1783 calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_2$, $\text{M} + \text{Na}^+$).

(S)-2-((R)-2,3-dihydro-1H-inden-1-yl)pyrrolidine (IV-102). A sample of crude product **IV-100** was dissolved in 2 mL CH_2Cl_2 and several drops of TFA were added and the reaction was stirred until consumption of the starting material by ^1H NMR analysis. GC analysis of the crude material revealed a 1: 9.7 (syn:anti) mixture of diastereomers, which was also confirmed by conversion to the *N*-Ph pyrrolidine **IV-90** via *N*-arylation of the pure **IV-102**. ^1H NMR (400 MHz, CDCl_3) δ 7.43–7.28 (m, 2 H), 7.24–7.10 (m, 2 H), 3.20–3.14 (m, 2 H), 3.11–3.06 (m, 2 H), 3.01–2.93 (m, 2 H), 2.88–2.80 (m, 2 H), 2.26–2.20 (m, 1 H), 1.92–1.81 (m, 2 H), 1.81–1.66 (m, 2 H); ^{13}C NMR (75 MHz, CDCl_3) δ 145.1, 144.4, 128.6, 126.7, 126.2, 125.0, 124.7, 63.0, 50.4, 46.9, 31.6, 30.0, 29.3, 25.2; IR (film) 2917, 1651 cm^{-1} . MS (ESI) 188.1431 (188.1439 calcd for $\text{C}_{13}\text{H}_{17}\text{N}$, $\text{M} + \text{H}^+$).

(S)-2-((S)-2,3-dihydro-1H-inden-1-yl)pyrrolidine (IV-103). A sample of crude product **IV-101** was dissolved in 2 mL CH_2Cl_2 and several drops of TFA were added and the reaction was stirred until consumption of the starting material by ^1H NMR analysis. GC analysis of the crude material revealed a 2.15:1.0 (syn: anti) mixture of diastereomers,

which was also confirmed by conversion to the *N*-Ph pyrrolidine **IV-89** via *N*-arylation of the pure **IV-103**. ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.27 (m, 1 H), 7.23–7.12 (m, 3 H), 3.26–3.18 (m, 2 H), 3.05–2.93 (m, 2 H), 2.89–2.79 (m, 2 H), 2.27–2.17 (m, 1 H), 2.05–1.93 (m, 3 H), 1.91–1.66 (m, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 145.0, 144.9, 128.6, 126.8, 126.24, 126.15, 124.8, 124.6, 62.4, 50.1, 46.4, 31.4, 30.4, 30.2, 29.3, 26.5, 25.6, 25.1; IR (film) 2930, 1688 cm⁻¹. MS (ESI) 188.1431 (188.1439 calcd for C₁₃H₁₇N, M + H⁺).

(±)-(1*S**,2*R**,5*R**)-*N*,5-Diphenyl-2-indan-1-ylpyrrolidine (**IV-104**). The cyclization of **IV-55** (123.8 mg, 0.295 mmol) following the general procedure using PCy₃·HBF₄ as ligand afforded 59 mg (59%) of the title compound as yellow foam. This compound was judged to be a 5:1 mixture of diastereomers **IV-104** and **IV-112** by ¹H NMR analysis. Data are for the major diastereomer. ¹H NMR (500 MHz, CDCl₃) δ 7.49–7.46 (m, 1 H), 7.41–7.36 (m, 2 H), 7.31–7.16 (m, 4 H), 7.14–7.10 (m, 4 H), 6.74–6.59 (m, 3 H), 5.17 (d, *J* = 6.8 Hz, 1 H), 4.87 (dd, *J* = 3.6, 8.0 Hz, 1 H), 4.14 (dt, *J* = 3.6, 7.2 Hz, 1 H), 2.98–2.90 (m, 1 H), 2.87–2.79 (m, 1 H) 2.65–2.54 (m, 1 H), 2.16–2.01 (m, 2 H), 1.97–1.90 (m, 1 H), 1.85–1.80 (m, 1 H), 1.66–1.61 (m, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 145.5, 145.3, 145.1, 144.9, 129.0, 128.6, 126.7, 126.6, 126.42, 126.39, 124.8, 123.9, 116.0, 115.0, 63.4, 61.1, 45.3, 35.3, 31.9, 27.4, 24.7; IR (film) 2963 cm⁻¹. Anal calcd for C₂₅H₂₅N: C, 88.45; H, 7.42; N, 4.13. Found: 88.16; H, 7.46; N, 4.13.

(±)-(1*S**,2*S**,5*R**)-*N*,5-Diphenyl-2-indan-1-yl-pyrrolidine (**IV-110**). The cyclization of **IV-63** (100 mg, 0.24 mmol) following the general procedure using PCy₃·HBF₄ as ligand afforded 60 mg (75%) of the title compound as an orange solid, m.p. 114–119 °C. This

compound was judged to be a 2:1 mixture of diastereomers **IV-110** and **IV-111** by ^1H analysis. ^1H NMR (500 MHz, CDCl_3) δ 7.38–7.35 (m, 4 H), 7.34–7.29 (m, 2 H), 7.25–7.20 (m, 2 H), 7.16–7.13 (m, 3 H), 6.71 (t, $J = 7.0$ Hz, 1 H), 6.67 (d, $J = 8.0$ Hz, 2 H), 4.60 (t, $J = 7.5$ Hz, 1 H), 4.05 (dt, $J = 2.0, 8.5$ Hz, 1 H), 3.49 (dt, $J = 3.5, 12.0$ Hz, 1 H), 3.22–3.15 (m, 1 H), 2.95–2.89 (m, 1 H), 2.52–2.47 (m, 1 H), 2.44–2.40 (m, 1 H), 2.39–2.31 (m, 1 H), 2.10–2.06 (m, 1 H), 2.05–1.92 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 149.8, 145.5, 145.3, 144.9, 129.0, 128.9, 127.1, 126.8, 126.2, 125.8, 125.7, 125.0, 117.1, 113.8, 67.3, 64.8, 50.2, 35.0, 31.6, 29.8, 28.9. IR (film) 2941, 1598 cm^{-1} . Anal calcd for $\text{C}_{25}\text{H}_{25}\text{N}$: C, 88.45; H, 7.42; N, 4.13. Found: C, 88.39; H, 7.40; N, 4.17.

Determination of Stereochemistry

The stereochemistry of 2-(1-indanyl)tetrahydrofuran products **IV-64** and **IV-65** was assigned by preparing the related tetrahydrofurans **IV-74** and **IV-76** with subsequent conversion of **IV-74** to the crystalline solid **IV-75** (Scheme 49). Connectivity of **IV-64**–**IV-65** and **IV-74** and **IV-76** was determined by 2D-NMR COSY and HSQC experiments, and the stereochemical configuration of **IV-75** was established by X-ray crystallography. The unit cell contained both enantiomers of the racemic product. Tetrahydrofuran derivatives **IV-74** and **IV-76** were prepared using a sequence of reactions similar to those described above for the synthesis of **IV-64** and **IV-65**.

Z-7-[5-(Benzhydrylideneamino)-2-bromophenyl]hept-4-en-1-ol (IV-73). ^1H NMR (500 MHz, CDCl_3) δ 7.73–7.71 (m, 2 H), 7.49–7.46 (m, 1 H), 7.42–7.39 (m, 1 H) 7.33–7.26 (m, 5 H), 7.11–7.09 (m, 2 H), 6.60 (d, $J = 2.5$ Hz, 1 H), 6.43 (dd, $J = 2.5, 8.5$ Hz, 1 H), 5.37–5.30 (m, 2 H), 3.61–3.58 (m, 2 H), 2.63–2.60 (m, 2 H), 2.24–2.19 (m, 2 H),

2.09–2.05 (m, 2 H), 1.60–1.53 (m, 2 H), 1.49 (s, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.1, 150.6, 141.3, 139.6, 136.2, 132.8, 131.1, 130.2, 129.6, 129.5, 129.1, 129.0, 128.5, 128.3, 123.4, 120.7, 118.6, 62.7, 36.1, 32.8, 24.5, 23.8. IR (film) 3370, 2933, 1614 cm^{-1} ; MS (ESI) 470.1093 (470.1095 calcd for $\text{C}_{26}\text{H}_{26}\text{BrNO}$, $\text{M} + \text{Na}^+$).

(±)-(1*S,2*S**)-Benzhydrylidene[1-(tetrahydrofuran-2-yl)indan-5-yl]amine (IV-76).** ^1H NMR (400 MHz, CDCl_3) δ 7.73–7.71 (m, 2 H), 7.47–7.43 (m, 3 H), 7.40–7.36 (m, 2 H), 7.24–7.21 (m, 2 H), 7.13–7.11 (m, 2 H), 6.58 (s, 1 H), 6.49 (dd, $J = 2.0, 8.0$ Hz, 1 H), 3.91–3.85 (m, 2 H), 3.79–3.74 (m, 1 H), 3.22–3.16 (m, 1 H), 2.79–2.67 (m, 2 H) 2.16–2.04 (m, 1 H), 1.89–1.79 (m, 3 H), 1.74–1.65 (m, 1 H), 1.54–1.48 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.8, 150.1, 144.8, 140.4, 140.2, 136.7, 130.7, 129.8, 129.5, 128.6, 128.3, 128.0, 125.2, 119.3, 117.2, 83.4, 68.3, 49.2, 31.8, 29.6, 28.3, 25.9; IR (film) 2953, 1652 cm^{-1} . Anal calcd for $\text{C}_{26}\text{H}_{25}\text{NO}$: C, 84.98; H, 6.86; N, 3.81. Found: C, 84.92; H, 6.84; N, 3.71.

(±)-(1*S,2*R**)-Benzhydrylidene[1-(tetrahydrofuran-2-yl)indan-5-yl]amine (IV-74).** ^1H NMR (400 MHz, CDCl_3) δ 7.72 (d, $J = 7.2$ Hz, 2 H), 7.47–7.44 (m, 1 H), 7.41–7.37 (m, 2 H), 7.34–7.30 (m, 1 H), 7.27–7.24 (m, 2 H), 7.13–7.11 (m, 2 H), 7.03 (d, $J = 7.6$ Hz, 1 H), 6.61 (s, 1 H), 6.46 (d, $J = 8.4$ Hz, 1 H), 3.90–3.84 (m, 1 H), 3.84–3.79 (m, 1 H), 3.74–3.68 (m, 1 H), 3.27–3.22 (m, 1 H), 2.82–2.77 (m, 1 H), 2.72–2.66 (m, 1 H), 2.20–2.15 (m, 1 H), 1.97–1.87 (m, 2 H), 1.86–1.77 (m, 2 H), 1.63–1.46 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.9, 150.3, 145.6, 140.2, 138.9, 136.7, 130.7, 129.8, 129.5, 128.6, 128.4, 128.0, 124.9, 119.1, 117.4, 82.1, 68.1, 49.2, 31.4, 29.1, 28.7, 26.4; IR (film) 2942, 1652 cm^{-1} ; MS (EI) 367.1942 (367.1936 calculated for $\text{C}_{26}\text{H}_{25}\text{NO}$).

(±)-(1*S,2*R**)-Biphenyl-4-yl[1-(tetrahydrofuran-2-yl)indan-5-yl]amine (IV-75).** ¹H NMR (400 MHz, CDCl₃) δ 7.58–7.55 (m, 2 H), 7.51–7.48 (m, 2 H), 7.44–7.40 (m, 3 H), 7.31–7.28 (m, 1 H), 7.12–7.08 (m, 2 H), 7.01 (s, 1 H), 6.95–6.93 (m, 1 H), 5.73 (s, br, 1 H), 4.00–3.94 (m, 1 H), 3.93–3.88 (m, 1 H), 3.83–3.78 (m, 1 H), 3.27–3.21 (m, 1 H), 2.95–2.81 (m, 2 H), 2.26–2.17 (m, 1 H), 2.03–1.85 (m, 3 H), 1.82–1.73 (m, 1 H), 1.65–1.56 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 145.8, 143.6, 141.6, 141.2, 139.1, 133.2, 128.9, 128.1, 126.7, 126.6, 126.4, 117.5, 117.3, 114.8, 83.3, 68.3, 49.4, 32.0, 30.0, 28.7, 25.9; IR (film) 2951, 1605 cm⁻¹; MS (EI): 355.1924 (355.1936 calculated for C₂₅H₂₅NO); mp 87–90 °C.

The stereochemistry of the 2-(1-indanyl)tetrahydrofuran products **IV-77** and **IV-78** was established by comparison of the ¹H NMR spectra of **IV-77** and **IV-78** to the related tetrahydrofuran derivatives **IV-81** and **IV-82**, which were in turn assigned by X-ray crystallographic analysis of **IV-81**. The connectivity of these molecules was further confirmed by 2D-NMR COSY and HSQC experiments. Biphenyl tetrahydrofuran derivatives **IV-79** and **IV-80** were prepared using a sequence of reactions analogous to those described above for the synthesis of **IV-58** and **IV-50**.

***E*-1,1-Bis(biphenyl-4-yl)-7-(2-bromophenyl)hept-4-en-1-ol (IV-80).** ¹H NMR (500 MHz, CDCl₃) δ 7.63–7.59 (m, 8 H), 7.56–7.54 (m, 5 H), 7.47–7.46 (m, 4 H) 7.38–7.35 (m, 2 H), 7.26–7.20 (m, 2 H), 7.09–7.05 (m, 1 H), 5.58–5.50 (m, 2 H), 2.83–2.80 (m, 2 H), 2.45–2.42 (m, 2 H), 2.36–2.31 (m, 2 H), 2.12–2.10 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 146.1, 141.4, 140.9, 139.9, 132.9, 131.1, 130.6, 129.8, 128.9, 127.7, 127.5,

127.4, 127.2, 127.1, 126.6, 124.7, 78.4, 41.8, 36.4, 33.0, 27.3; IR (film) 3447, 2928 cm^{-1} . MS (EI) 572.1703 (572.1715 calcd for $\text{C}_{37}\text{H}_{33}\text{BrO}$).

Z-1,1-Bis(biphenyl-4-yl)-7-(2-bromophenyl)hept-4-en-1-ol (IV-79). ^1H NMR (500 MHz, CDCl_3) δ 7.59–7.55 (m, 8 H), 7.51–7.44 (m, 5 H), 7.44–7.41 (m, 4 H) 7.35–7.32 (m, 2 H), 7.13–7.10 (m, 2 H), 7.00–6.96 (m, 1 H), 5.53–5.45 (m, 2 H), 2.73–2.70 (m, 2 H), 2.29–2.23 (m, 4 H), 2.08–2.03 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 146.0, 141.2, 140.9, 139.9, 132.9, 130.8, 130.6, 129.3, 128.9, 127.8, 127.4, 127.3, 127.2, 126.6, 124.6, 78.4, 42.0, 36.3, 27.7, 22.2 (one carbon signal is absent due to accidental equivalence); IR (film) 3563, 2928 cm^{-1} . Anal calcd for $\text{C}_{37}\text{H}_{33}\text{BrO}$: C, 77.48; H, 5.80. Found: C, 77.51; H, 5.61.

(±)-(1R*,5S*)-2,2-Bis(biphenyl-4-yl)-5-indan-1-yltetrahydrofuran (IV-82). ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, $J = 6.8$ Hz, 1 H), 7.62–7.50 (m, 12 H), 7.43–7.40 (m, 4 H), 7.34–7.31 (m, 2 H), 7.25–7.22 (m, 3 H), 4.30–4.25 (m, 1 H), 3.51–3.45 (m, 1 H), 2.99–2.87 (m, 2 H), 2.76–2.62 (m, 2 H), 2.26–2.18 (m, 1 H), 2.12–2.04 (m, 1 H), 1.88–1.72 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 146.6, 146.0, 145.7, 144.7, 141.11, 141.09, 139.8, 139.7, 128.9, 127.4, 127.3, 127.28, 127.23, 127.1, 126.9, 126.5, 126.46, 126.42, 126.1, 124.5, 88.4, 83.0, 50.6, 39.1, 31.9, 30.3, 28.7; IR (film) 3027, 2948 cm^{-1} ; MS (EI): 492.2445 (492.2453 calculated for $\text{C}_{26}\text{H}_{25}\text{NO}$); m.p. 155–159 $^{\circ}\text{C}$.

(±)-(1S*,5S*)-2,2-Bis(biphenyl-4-yl)-5-indan-1-yltetrahydrofuran (IV-81). ^1H NMR (400 MHz, CDCl_3) δ 7.64–7.55 (m, 13 H), 7.46–7.42 (m, 4 H), 7.36–7.28 (m, 3 H), 7.21–7.17 (m, 1 H), 7.14–7.11 (m, 1 H), 4.28–4.22 (m, 1 H), 3.52–3.47 (m, 1 H), 3.10–3.02 (m, 1 H), 2.95–2.87 (m, 1 H), 2.81–2.75 (m, 1 H), 2.62–2.55 (m, 1 H), 2.42–2.26 (m, 2

H), 2.15–2.07 (m, 1 H), 1.97–1.88 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.5, 146.0, 145.3, 144.1, 141.11, 141.08, 139.8, 139.6, 128.9, 127.4, 127.3, 127.27, 127.25, 127.1, 127.0, 126.5, 126.4, 126.1, 125.1, 124.7, 87.6, 81.2, 50.4, 39.2, 31.4, 29.9, 28.9; MS (EI) 492.2448 (492.2453 calcd for $\text{C}_{37}\text{H}_{32}\text{O}$); m.p. 145–147 °C.

The stereochemistry of the 2-(1-indanyl)tetrahydrofuran product **IV-83** was established by comparison of the ^1H NMR spectra of **IV-83** to the related tetrahydrofuran derivative **88**, which was in turn assigned by X-ray crystallographic analysis. The connectivity of these molecules was further confirmed by 2D-NMR COSY and HSQC experiments. Derivative **IV-88** was prepared by oxidation of **IV-73** followed by addition of phenylmagnesium bromide.

***E*-7-[5-(Benzhydrylideneamino)-2-bromophenyl]-1-phenylhept-4-en-1-ol (IV-87).** ^1H NMR (500 MHz, CDCl_3) δ 7.60–7.60 (m, 2 H), 7.47–7.44 (m, 1 H), 7.38–7.29 (m, 8 H) 7.28–7.23 (m, 3 H), 7.07–7.05 (m, 2 H), 6.65 (d, $J = 3.0$ Hz, 1 H), 6.31 (dd, $J = 2.5, 8.5$ Hz, 1 H), 5.46–5.30 (m, 2 H), 4.52–4.48 (m, 1 H), 2.75–2.69 (m, 1 H), 2.63–2.57 (m, 2 H), 2.23–2.05 (m, 4 H), 1.87–1.80 (m, 1 H), 1.71–1.64 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.4, 150.2, 145.5, 141.3, 136.1, 132.7, 131.2, 130.8, 130.1, 129.64, 129.60, 129.1, 129.0, 128.6, 128.5, 128.4, 127.5, 126.1, 124.0, 120.3, 73.4, 38.7, 36.2, 32.8, 29.0; IR (film) 3392, 2926 cm^{-1} . MS (EI) 523.1506 (523.1511 calcd for $\text{C}_{32}\text{H}_{30}\text{BrNO}$).

(\pm)-(1*S,2*R**,5*R**)-Benzhydrylidene[1-(5-phenyltetrahydrofuran-2-yl)indan-5-yl]amine (IV-88).** ^1H NMR (400 MHz, CDCl_3) δ 7.74–7.71 (m, 2 H), 7.47–7.44 (m, 1 H), 7.41–7.37 (m, 2 H), 7.33–7.30 (m, 5 H), 7.27–7.22 (m, 6 H), 7.21–7.12 (m, 2 H),

5.05–5.02 (m, 1 H), 4.28–4.23 (m, 1 H), 3.39–3.28 (m, 1 H), 2.80–2.73 (m, 2 H), 2.39–2.32 (m, 1 H), 2.20–2.12 (m, 1 H), 2.03–1.97 (m, 1 H), 1.86–1.70 (m, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.8, 150.2, 144.9, 144.3, 140.4, 140.2, 136.7, 130.7, 129.8, 129.5, 128.6, 128.5, 128.4, 128.0, 127.2, 125.7, 125.4, 119.3, 117.2, 84.1, 80.8, 49.6, 35.4, 31.9, 29.9, 28.2; IR (film) 2926 cm^{-1} ; MS (EI) 443.2255 (443.2249 calculated for $\text{C}_{32}\text{H}_{29}\text{NO}$); m.p. 117–121 °C.

The stereochemistry of the 2-(1-indanyl)pyrrolidine products **IV-89** and **IV-90** was established by comparison of the ^1H NMR spectra of **IV-89** and **IV-90** to the analogous *N*-biphenyl pyrrolidine derivatives **IV-95** and **IV-96**, which were in turn assigned by X-ray crystallographic analysis. The connectivity of these four molecules was confirmed by 2D-NMR COSY and HSQC experiments. Biphenyl pyrrolidine derivatives **IV-95**–**IV-96** were prepared using a sequence of reactions analogous to those described above for the synthesis of **IV-89** and **IV-90**.

(E)-Biphenyl-4-yl-[7-(2-bromophenyl)hept-4-enyl]amine (IV-94). ^1H NMR (400 MHz, CDCl_3) δ 7.59–7.55 (m, 3 H), 7.49–7.46 (m, 2 H), 7.44–7.40 (m, 2 H) 7.30–7.22 (m, 3 H), 7.09–7.05 (m, 1 H), 6.71–6.67 (m, 2 H), 5.60–5.46 (m, 2 H), 3.75 (s, 1 H), 3.16 (t, $J = 5.6\text{ Hz}$, 2 H), 2.86–2.82 (m, 2 H), 2.39–2.34 (m, 2 H), 2.18–2.12 (m, 2 H), 1.75–1.68 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.0, 141.5, 141.4, 132.9, 130.6, 130.5, 130.2, 130.0, 128.8, 128.1, 127.7, 127.5, 126.4, 126.2, 124.7, 113.1, 43.5, 36.4, 32.9, 30.2, 29.3; IR (film) 3410, 2928, 1612 cm^{-1} ; MS (ESI) 420.1333 (420.1327 calcd for $\text{C}_{25}\text{H}_{26}\text{BrN}$, $\text{M} + \text{H}^+$).

(Z)-Biphenyl-4-yl-[7-(2-bromophenyl)hept-4-enyl]amine (IV-92). ¹H NMR (400 MHz, CDCl₃) δ 7.56–7.53 (m, 3 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 7.40 (t, *J* = 7.6 Hz, 3 H), 7.28–7.18 (m, 2 H), 7.08–7.04 (m, 1 H), 6.67 (d, *J* = 8.8 Hz, 2 H), 5.55–5.42 (m, 2 H), 3.72 (s, br, 1 H), 3.12 (t, *J* = 7.2 Hz, 2 H), 2.82–2.78 (m, 2 H), 2.43–2.37 (m, 2 H), 2.15–2.10 (m, 2 H), 1.65–1.57 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 148.0, 141.5, 141.3, 133.0, 130.8, 130.23, 130.19, 129.3, 128.8, 128.1, 127.8, 127.5, 126.5, 126.2, 124.6, 113.2, 43.7, 36.4, 29.5, 27.8, 25.0; IR (film) 3411, 2859, 1612 cm⁻¹. Anal calcd for C₂₅H₂₆BrN: C, 71.43; H, 6.23; N, 3.33. Found: C, 71.67; H, 6.18; N, 3.39.

(±)-(1R*,2S*)-N-(4-Phenyl)phenyl-2-indan-1-ylpyrrolidine (IV-96). ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J* = 8.4 Hz, 2 H), 7.50–7.48 (m, 2 H), 7.41 (t, *J* = 8.0 Hz, 2 H), 7.30–7.20 (m, 3 H), 7.20–7.14 (m, 2 H), 6.72 (d, *J* = 8.4 Hz, 2 H), 4.38–4.34 (m, 1 H), 3.90–3.85 (m, 1 H), 3.69–3.64 (m, 1 H), 3.39–3.32 (m, 1 H), 3.02–2.95 (m, 1 H), 2.90–2.82 (m, 1 H), 2.13–2.04 (m, 2 H), 2.02–1.87 (m, 3 H), 1.74–1.68 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 147.4, 145.0, 144.9, 141.6, 128.8, 128.7, 127.9, 126.8, 126.4, 126.3, 126.0, 124.7, 124.4, 112.9, 60.9, 50.2, 46.9, 31.8, 27.8, 27.3, 24.5; IR (film) 2940, 1609 cm⁻¹; MS (EI): 339.1989 (339.1987 calcd for C₂₅H₂₅N); m.p. 103–110 °C.

(±)-(1R*,2R*)-N-(4-Phenyl)phenyl-2-indan-1-ylpyrrolidine (IV-95). ¹H NMR (400 MHz, CDCl₃) δ 7.56–7.54 (m, 4 H), 7.41 (t, *J* = 8.0 Hz, 2 H), 7.28–7.21 (m, 2 H), 7.18–7.14 (m, 1 H), 7.01–7.07 (m, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 4.11–4.08 (m, 1 H), 3.97–3.93 (m, 1 H), 3.51–3.45 (m, 1 H), 3.27–3.20 (m, 1 H), 3.10–3.04 (m, 1 H), 2.97–2.89 (m, 1 H), 2.39–2.31 (m, 1 H), 1.98–1.87 (m, 2 H), 1.72–1.55 (m, 2 H), 1.34–1.27 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 147.1, 145.1, 144.2, 141.6, 128.8, 128.6, 128.0,

126.9, 126.4, 126.2, 126.0, 125.9, 124.5, 112.9, 63.0, 50.3, 45.6, 32.0, 28.2, 27.6, 24.1; IR (film) 2941, 1609 cm^{-1} ; MS (EI): 339.1994 (339.1987 calculated for $\text{C}_{25}\text{H}_{25}\text{N}$); m.p. 93–98 °C.

The stereochemistry for (\pm) -(1*S**,2*S**,5*R**)-*N*,5-Diphenyl-2-indan-1-yl-pyrrolidine (**IV-10**) was established by X-ray crystallographic analysis as shown below. Data are given above.

The stereochemistry of (1*S**,2*R**,5*R**)-*N*,5-Diphenyl-2-indan-1-ylpyrrolidine (**IV-104**) was established by comparison of the ^1H NMR spectra of **IV-104** to that obtained for the analogous *N*-biphenyl pyrrolidine derivative **IV-108**, which was in turn assigned by X-ray crystallographic analysis. Derivative **IV-108** was prepared using a sequence of reactions analogous to those described above for the synthesis of **IV-104**.

***E*-Biphenyl-4-yl[7-(2-bromophenyl)-1-phenylhept-4-enyl]amine (IV-107).** ^1H NMR (400 MHz, CDCl_3) δ 7.54–7.51 (m, 1 H), 7.49–7.47 (m, 2 H), 7.37–7.31 (m, 8 H), 7.25–7.18 (m, 4 H), 7.06–7.02 (m, 1 H), 6.58–6.55 (m, 2 H), 5.55–5.43 (m, 2 H), 4.35 (t, $J = 6.8$ Hz, 1 H), 4.18 (s, br, 1 H), 2.80–2.77 (m, 2 H), 2.35–2.29 (m, 2 H), 2.15–2.03 (m, 2 H), 1.93–1.80 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.0, 144.1, 141.4, 141.3, 132.9, 130.6, 130.3, 130.24, 130.19, 128.78, 128.77, 128.0, 127.7, 127.5, 127.2, 126.6, 126.4, 126.1, 124.7, 113.6, 57.8, 38.6, 36.4, 32.9, 29.5; IR (film) 3413, 2930, 1612 cm^{-1} . MS (ESI) 496.1646 (496.1640 calcd for $\text{C}_{31}\text{H}_{30}\text{BrN}$, $\text{M} + \text{H}^+$).

(1*S,2*R**,5*R**)-*N*-(Biphenyl-4-yl)-2-indan-1-yl-5-phenylpyrrolidine (IV-108).** ^1H NMR (400 MHz, CDCl_3) δ 7.49–7.47 (m, 3 H), 7.38–7.32 (m, 6 H), 7.26–7.16 (m, 5 H),

7.13–7.11 (m, 2 H), 6.70 (d, $J = 8.8$ Hz, 2 H), 5.18 (d, $J = 8$ Hz, 1 H), 4.89–4.86 (m, 1 H), 4.17–4.12 (m, 1 H), 2.98–2.87 (m, 1 H), 2.86–2.78 (m, 1 H), 2.65–2.54 (m, 1 H), 2.13 – 2.01 (m, 2 H), 1.96–1.89 (m, 1 H), 1.85–1.80 (m, 1 H), 1.66–1.61 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 145.2, 145.1, 144.9, 144.8, 141.3, 128.8, 128.7, 127.6, 126.8, 126.7, 126.5, 126.4, 126.3, 126.0, 124.9, 123.9, 115.1, 114.5, 63.5, 61.2, 45.4, 35.3, 31.9, 27.5, 24.7; IR (film) 2918, 1609 cm^{-1} . MS (ESI) 416.2370 (416.2378 calcd for $\text{C}_{31}\text{H}_{29}\text{N}$, $\text{M} + \text{H}^+$); mp 148–152 $^\circ\text{C}$.

(Schemes 69–73)

The substrates and products described in (Schemes 69–73) were prepared using analogous transformations and procedures as those discussed in the first part of the experimental (pages 229-252) for the intramolecular carboetherification and carboamination reactions.

1-(allyloxy)-2-bromobenzene (IV-157). ^1H NMR (500 MHz, CDCl_3) δ 7.55–7.53 (dd, $J = 1.5, 6.4$ Hz, 1 H), 7.26–7.23 (m, 2 H), 6.90 (dd, $J = 1.5, 8.5$ Hz, 1 H), 6.84 (dt, $J = 1.0, 8.0$ Hz, 1 H), 6.11–6.03 (m, 1 H), 5.51–5.47 (m, 1 H), 5.33–5.30 (m, 1 H), 4.62–4.61 (m, 1 H).

1-(allyloxy)-2-iodobenzene (IV-158). ^1H NMR (300 MHz, CDCl_3) δ 7.78 (dd, $J = 1.8, 8.1$ Hz, 1 H), 7.31–7.25 (m, 1 H), 6.81 (dd, $J = 1.2, 8.1$ Hz, 1 H), 6.71 (dt, $J = 1.5, 7.8$ Hz, 1 H), 6.13–6.00 (m, 1 H), 5.56–5.49 (m, 1 H), 5.34–5.29 (m, 1 H), 4.61–4.59 (m, 2 H).

2-(2-bromophenoxy)acetaldehyde (IV-159). ^1H NMR (500 MHz, CDCl_3) 9.91 (s, 1 H), 7.60–7.52 (m, 1 H), 6.93–6.78 (m, 3 H), 4.61 (s, 2 H).

2-(2-iodophenoxy)acetaldehyde (IV-160). ^1H NMR (300 MHz, CDCl_3) ^1H NMR (300 MHz, CDCl_3) δ 9.92 (s, 1 H), 7.84–7.72 (m, 1 H), 7.33–7.28 (m, 1 H), 6.85–6.69 (s, 2 H), 4.61 (s, 2 H).

(Z)-ethyl 6-(2-bromophenoxy)hex-4-enoate (IV-161). ^1H NMR (400 MHz, CDCl_3) δ 7.54–7.52 (m, 1 H), 7.26–7.22 (m, 1 H), 6.91 (d, $J = 8$ Hz, 1 H), 6.85–6.81 (m, 1 H), 5.80–5.74 (m, 1 H), 5.67–5.61 (m, 1 H), 4.68 (d, $J = 6$ Hz, 2 H), 4.13 (q, $J = 7.2$ Hz, 2 H), 2.49–2.38 (m, 4 H), 1.25 (t, $J = 7.2$ Hz, 3 H).

(Z)-ethyl 6-(2-iodophenoxy)hex-4-enoate (IV-162). ^1H NMR (400 MHz, CDCl_3) δ 7.55–7.49 (m, 1 H), 7.33–7.24 (m, 1 H), 6.82 (d, $J = 8.4$ Hz, 1 H), 6.71–6.67 (m, 1 H), 5.82–5.72 (m, 1 H), 5.66–5.54 (m, 1 H), 4.66 (d, $J = 6.4$ Hz, 2 H), 4.15–4.03 (m, 2 H), 2.49–2.30 (m, 4 H), 1.24 (t, $J = 5.6$ Hz, 3 H).

(Z)-N-(6-(2-bromophenoxy)hex-4-enyl)aniline (IV-163). ^1H NMR (400 MHz, CDCl_3) δ 7.56–7.53 (m, 1 H), 7.30–7.15 (m, 3 H), 6.97–6.82 (m, 2 H), 6.69 (t, $J = 7.2$ Hz, 1 H), 6.59 (d, $J = 8.4$ Hz, 2 H), 5.82–5.67 (m, 2 H), 4.65 (d, $J = 6$, 1 H), 4.58 (d, $J = 6$ Hz, 1 H), 3.64 (s, 1 H), 3.20–3.12 (m, 2 H), 2.31–2.25 (m, 2 H), 1.78–1.71 (m, 2 H).

(Z)-6-(2-bromophenoxy)-N-phenylhex-4-enamide (IV-163b). ^1H NMR (400 MHz, CDCl_3) δ 7.55–7.49 (m, 2 H), 7.31 (t, $J = 8$ Hz, 2 H), 7.25–7.21 (m, 2 H), 7.10 (t, $J = 7.2$ Hz, 1 H), 6.92 (d, $J = 8.4$ Hz, 1 H), 6.84 (dt, $J = 1.2, 7.6$ Hz, 1 H), 5.86–5.80 (m, 1 H), 5.78–5.71 (m, 1 H), 4.70 (d, $J = 5.6$ Hz, 1 H), 3.76–3.73 (m, 1H), 2.62–2.56 (m, 2H), 2.49–2.45 (m, 2H), 1.87–1.84 (m, 1 H).

(Z)-N-(6-(2-iodophenoxy)hex-4-enyl)aniline (IV-164). ^1H NMR (400 MHz, CDCl_3) δ 7.31–7.27 (m, 1 H), 7.19–7.15 (m, 2 H), 6.98–6.89 (m, 3 H), 6.70 (t, $J = 7.2$ Hz, 1 H), 6.59 (d, $J = 8.8$ Hz, 2 H), 5.80–5.67 (m, 2 H), 4.58 (d, $J = 5.6$ Hz, 2H), 3.68 (t, $J = 6.4$ Hz, 2 H), 3.16 (t, $J = 7.2$ Hz, 1 H), 2.28 (q, $J = 7.2$ Hz, 2 H), 1.78–1.66 (m, 2 H).

(Z)-7-(2-bromophenoxy)-2-methylhept-5-en-2-ol (IV-165). ^1H NMR (400 MHz, CDCl_3) δ 7.54 (dd, $J = 1.6, 8$ Hz, 1 H), 7.27–7.23 (m, 1 H), 6.92 (dd, $J = 1.2, 8.4$ Hz, 1 H), 6.84 (dt, $J = 1.6, 7.6$ Hz, 1 H), 5.77–5.67 (m, 2 H), 4.68 (d, $J = 4.8$ Hz, 2H), 2.27–2.22 (m, 2 H), 1.60–1.56 (m, 3 H), 1.24 (s, 6 H).

(Z)-6-(2-iodophenoxy)hex-4-en-1-ol (IV-166). ^1H NMR (400 MHz, CDCl_3) δ 7.31–7.27 (m, 1 H), 6.98–6.91 (m, 3 H), 5.80–5.67 (m, 2 H), 4.60 (d, $J = 6.0$ Hz, 2 H), 3.68 (q, $J = 5.6$ Hz, 2 H), 2.27 (d, $J = 7.2$ Hz, 2 H), 1.73–1.66 (m, 2 H), 1.48 (t, $J = 5.6$ Hz, 1 H).

1-(2-bromophenyl)-1H-pyrrole (IV-172).⁴⁶ ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, $J = 8$ Hz, 1 H), 7.44–7.37 (m, 2 H), 7.30–7.26 (m, 1 H), 6.93–6.92 (m, 2 H), 6.39–6.38 (m, 2 H).

1-(2-bromophenyl)-1H-pyrrole-2-carbaldehyde (IV-173). ^1H NMR (400 MHz, CDCl_3) δ 9.54 (s, 1 H), 7.76–7.73 (m, 1 H), 7.49–7.45 (m, 1 H), 7.42–7.37 (m, 2 H), 7.18 (dd, $J = 1.6, 4$ Hz, 2 H), 7.01–7.00 (m, 1 H).

(Z)-ethyl 5-(1-(2-bromophenyl)-1H-pyrrol-2-yl)pent-4-enoate (IV-174). ^1H NMR (400 MHz, CDCl_3) δ 7.69 (dd, $J = 1.6, 4.4$ Hz, 1 H), 7.42–7.38 (m, 1 H), 7.34–7.27 (m, 2 H), 6.73–6.72 (m, 1 H), 6.45–6.43 (m, 1 H), 6.36 (t, $J = 3.6$, 1 H), 5.84–5.74 (m, 1 H), 5.39–

5.33 (m, 1 H), 4.14 (q, $J = 7.2$ Hz, 2 H), 2.74–2.69 (m, 2 H), 2.48–2.44 (m, 2 H), 1.26 (t, $J = 7.2$ Hz, 3 H).

(Z)-5-(1-(2-bromophenyl)-1H-pyrrol-2-yl)pent-4-en-1-ol (IV-175). ^1H NMR (400 MHz, CDCl_3) δ 7.70 (dd, $J = 1.2, 8$ Hz, 1 H), 7.46–7.28 (m, 3 H), 6.73–6.72 (m, 1 H), 6.45–6.43 (m, 2 H), 5.78–5.75 (m, 1 H), 5.44–5.38 (m, 1 H), 3.73–3.68 (m, 2 H), 2.53–2.46 (m, 2 H), 1.81–1.72 (m, 2 H), 1.65 (s, 1 H).

(E)-ethyl 4-(2-(2-bromobenzyl)cyclohexylidene)butanoate (IV-177). 2:1 mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.77–7.64 (m, 1 H), 7.56–7.43 (m, 2 H), 7.33–7.00 (m, 1 H), 4.96 (t, $J = 7.2$ Hz, 1 H), 4.13–4.06 (m, 2 H), 3.36–3.32 (m, 1 H), 2.98–2.93 (m, 1 H), 2.76–2.65 (m, 2 H), 2.58–2.52 (m, 1 H), 2.45–2.22 (m, 3 H), 2.16–1.92 (m, 2 H), 1.70–1.55 (m, 4 H), 1.26–1.22 (m, 4 H).

(E)-4-(2-(2-bromobenzyl)cyclohexylidene)-N-phenylbutanamide (IV-178). 2:1 mixture of diastereomers. Data are for the major isomer. ^1H NMR (500 MHz, CDCl_3) δ 7.53–7.45 (m, 3 H), 7.35–6.98 (m, 6 H), 5.04 (t, $J = 7.5$ Hz, 1 H), 3.35 (dd, $J = 5.1, 13.8$ Hz, 2 H), 3.02–2.91 (m, 2 H), 2.78–2.65 (m, 1 H), 2.59–2.52 (m, 1 H), 2.46–2.24 (m, 2 H), 2.20–1.98 (m, 2 H), 1.87–1.82 (m, 2 H), 1.75–1.48 (m, 4 H).

(E)-4-(2-(2-bromobenzyl)cyclohexylidene)-N-phenylbutanamide (IV-179). 2:1 mixture of diastereomers. Data are for the major isomer. ^1H NMR (500 MHz, CDCl_3) δ 7.52–7.50 (m, 1 H), 7.35–7.28 (m, 3 H), 7.19–7.08 (m, 4 H), 7.05–6.99 (m, 1 H), 6.58 (dd, $J = 1.5, 9$ Hz, 1 H), 5.01 (t, $J = 4.2$ Hz, 1H), 3.56 (s, 1 H), 3.03–2.98 (m, 2 H), 2.94–2.88 (m, 1 H), 2.78–2.73 (m, 1 H), 2.48–2.43 (m, 1 H), 2.33–2.26 (m, 1 H), 2.17–2.05 (m, 2 H), 1.75–1.67 (m, 1 H), 1.63–1.40 (m, 3 H), 1.54–1.25 (m, 4 H).

2-(2-bromobenzyl)cyclopentanone (IV-182).⁴⁷

A flame-dried flask was charged with 9.31 g (8.85 mL, 100 mmol) of cyclopentanone, *N,N*-dimethylhydrazine (11.85 g, 9.25 mL, 120 mmol), benzene (40 mL) and TFA (0.05 mL) and was then equipped with a magnetic stirbar, reflux condenser and Dean Stark trap. The reaction mixture was heated at reflux for 1 hour. Potassium carbonate was added to the cooled reaction mixture which was then filtered and concentrated *in vacuo*. The organic residue was then dissolved in diethyl ether and washed with brine, dried over sodium sulfate, and concentrated *in vacuo* providing 11.8 g (90%) of 2-cyclopentylidene-1,1-dimethylhydrazine as a yellow oil.

A flame-dried flask was charged with 2-cyclopentylidene-1,1-dimethylhydrazine (7.4 g, 58.6 mmol) and THF (117 mL) and cooled to 0 °C, whereupon a solution of Butyllithium in hexanes (38.5 mL, 61.53 mmol, 1.6 M) was added. The reaction mixture was stirred for 50 min at 0 °C. At this point 2-Bromobenzyl-bromide (15.1 g, 60.4 mmol) in 10 mL THF was added via cannula. The reaction was stirred for 12 h, quenched with 1M HCl, and stirred for 2h followed by extraction with ethyl acetate, washing with saturated sodium chloride, and dried over anhydrous sodium sulfate. The crude material was purified by column chromatography to yield 11.26 g (76%) of the title compound. ¹H NMR (500 MHz, CDCl₃) δ 7.53 (d, *J* = 8 Hz, 1 H), 7.24–7.19 (m, 2 H), 7.08–7.05 (m, 1 H), 3.33 (dd, *J* = 4.5, 14 Hz, 1 H), 2.64–2.60 (m, 1 H), 2.52–2.46 (m, 1 H), 2.39–2.33 (m, 1 H), 2.18–2.10 (m, 1 H), 2.08–1.96 (m, 2 H), 1.79–1.69 (m, 1 H), 1.62–1.54 (m, 1 H).

(E)-ethyl 4-(2-(2-bromobenzyl)cyclopentylidene)butanoate (IV-183). 2:1 mixture of inseparable diastereomers. Data are for the mixture. ^1H NMR (300 MHz, CDCl_3) δ 7.52 (d, $J = 7.8$ Hz, 1 H), 7.35–7.30 (m, 1 H), 7.24–7.16 (m, 1 H), 7.10–7.02 (m, 1 H), 5.22–5.17 (m, 1 H), 4.17–4.08 (m, 2 H), 3.15–2.97 (m, 2 H), 2.87–2.80 (m, 2 H), 2.65–2.49 (m, 2 H), 2.41–2.12 (m, 2 H), 1.81–1.64 (m, 2 H), 1.61–1.48 (m, 3 H), 1.25 (t, $J = 7.2$ Hz, 3 H).

(E)-4-(2-(2-bromobenzyl)cyclopentylidene)butan-1-ol (IV-184). 2:1 mixture of inseparable diastereomers. Data are for the mixture. ^1H NMR (400 MHz, CDCl_3) δ 7.52 (d, $J = 8$ Hz, 1 H), 7.23–7.16 (m, 2 H), 7.07–7.02 (m, 1 H), 5.27–5.23 (m, 1 H), 3.66–3.58 (m, 2 H), 3.11–3.00 (m, 1 H), 2.88–2.82 (m, 1 H), 2.69–2.52 (m, 1 H), 2.47–2.40 (m, 1 H), 2.32–2.19 (m, 1 H), 2.11–2.02 (m, 1 H), 1.97–1.88 (m, 1 H), 1.80–1.71 (m, 1 H), 1.67–1.47 (m, 5 H), 1.40–1.24 (m, 2 H).

(E)-N-(4-(2-(2-bromobenzyl)cyclopentylidene)butyl)aniline (IV-186). 2:1 mixture of inseparable diastereomers. Data are for the mixture. ^1H NMR (300 MHz, CDCl_3) δ 7.59 (d, $J = 8.1$ Hz, 1 H), 7.40–7.36 (m, 1 H), 7.29–7.20 (m, 3 H), 7.13–7.08 (m, 1 H), 6.78–6.72 (m, 1 H), 6.68–6.64 (m, 2 H), 5.35–5.26 (m, 1 H), 3.64 (s, 1 H), 3.19–3.08 (m, 3 H), 2.95–2.78 (m, 1 H), 2.71–2.48 (m, 1 H), 2.39–2.26 (m, 1 H), 2.26–2.08 (m, 1 H), 2.05–1.96 (m, 1 H), 1.92–1.76 (m, 2 H), 1.76–1.55 (m, 5 H); ^{13}C NMR (75 MHz, CDCl_3) δ 148.6, 146.6, 146.1, 140.9, 140.5, 134.0, 133.8, 132.9, 131.9, 131.4, 129.4, 128.9, 128.7, 128.6, 127.8, 127.6, 127.3, 127.2, 125.0, 121.5, 120.1, 117.23, 117.18, 112.9, 112.8, 44.5, 43.8, 41.2, 40.4, 40.2, 32.8, 32.5, 31.3, 29.9, 29.5, 29.4, 27.2, 27.0, 24.0, 23.5; IR (film) 3413, 2948, 1603 cm^{-1} . MS (ESI) 384.1321 (384.1327 calcd for $\text{C}_{22}\text{H}_{26}\text{BrN}$, $\text{M} + \text{Na}^+$).

(2S)-2-((8aS)-1,2,3,3a,8,8a-hexahydrocyclopenta[a]inden-3a-yl)-1-phenylpyrrolidine (IV-187). The cyclization of **IV-186** (45 mg, 0.117 mmol) following the general procedure using $\text{PCy}_3 \cdot \text{HBF}_4$ as ligand afforded 18 mg (50%) of the title compound as a colorless oil. This compound was judged to be a 22:1 mixture of diastereomers by ^1H NMR analysis analysis. ^1H NMR (400 MHz, CDCl_3) δ 7.25–7.21 (m, 2 H), 7.19–7.10 (m, 4 H), 6.86 (d, $J = 7.6$ Hz, 2 H), 6.69 (t, $J = 7.6$ Hz, 1 H), 4.27–4.25 (m, 1 H), 3.50–3.45 (m, 1 H), 3.37–3.31 (m, 1 H), 3.13–3.06 (m, 1 H), 2.68–2.56 (m, 2 H), 2.21–2.14 (m, 1 H), 2.05–1.93 (m, 1 H), 1.85–1.75 (m, 3 H), 1.63–1.52 (m, 2 H), 1.35–1.19 (m, 2 H), 1.06–0.93 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 150.5, 148.6, 144.5, 129.0, 127.0, 126.6, 125.3, 124.5, 116.1, 113.7, 68.0, 64.9, 52.8, 46.6, 40.2, 39.2, 36.3, 29.0, 26.4, 24.0; IR (film) 2941, 1597 cm^{-1} . MS (ESI) 304.2057 (304.2065 calcd for $\text{C}_{22}\text{H}_{25}\text{N}$, $\text{M} + \text{Na}^+$).

5-(2-bromobenzyl)cyclopent-2-enone (IV-189).⁴⁸ A flame-dried flask was charged with diisopropylamine (6.04 g, 4.35 mL, 30.9 mmol) and THF (103 mL) and cooled to 0 °C, whereupon a solution of Butyllithium in hexanes (19.3 mL, 30.94 mmol, 1.6 M) was added. The reaction mixture was stirred for 40 min at 0 °C. At this point a solution of 2-(2-bromobenzyl)cyclopentanone in THF (10.3 mL) was added and the reaction mixture was stirred for an additional 20 min. This was followed by the addition of a solution of phenyl selenium bromide (7.3 g, 30.94 mmol) in 21 mL THF via cannula in one portion. This was followed by an immediate decolorization followed by stirring 5-10 min. The reaction mixture was then added to 0.5 M HCl/1:1 mixture of ether:pentanes and was then extracted with ethyl acetate and washed with brine, dried over sodium sulfate and purified by column chromatography.

The purified phenyl selenide was dissolved in CH₂Cl₂ (97 mL) and pyridine was added (3.9 mL). This solution was added to a mixture of 30% H₂O₂ (5.30 mL) in H₂O (5.30 mL) over a 10 min period at 0 °C (**Caution: no more than 10% of the H₂O₂ solution was added prior to commencement of oxidation**). After stirring for an additional 10 min at room temperature, the reaction mixture was poured into CH₂Cl₂ and 20 ml of 10% Na₂CO₃ with stirring. The aqueous layer was washed with 50 ml of CH₂Cl₂. The combined organic layers were washed with 50 ml of saturated NaCl solution and dried over Na₂SO₄, and concentrated *in vacuo* to provide the crude compound which was purified by column chromatography to provide 3.8 g (79%) of the title compound as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.68–7.66 (m, 1 H), 7.55 (dd, *J* = 1, 8.5 Hz, 1 H), 7.24–7.22 (m, 2 H), 7.11–7.07 (m, 1 H), 6.24–6.22 (m, 1 H), 3.36 (dd, *J* = 4, 13.5 Hz, 1 H), 2.82–2.77 (m, 1 H), 2.75–2.67 (m, 2 H), 2.50–2.45 (m, 2 H).

5-(2-bromobenzyl)cyclopent-2-enol (IV-190).⁴⁹ A flame-dried flask was charged with 5-(2-bromobenzyl)cyclopent-2-enone (1 g, 3.98 mmol) and THF (4 mL) and cooled to 0 °C, whereupon a solution of 9-BBN in THF (8 mL, 4.00 mmol, 0.5 M) was added via syringe pump over 5 h. Methanol was added to destroy the excess borane and the reaction mixture was then concentrated. The reaction mixture was diluted with pentane and 2-aminoethanol (244 μL, 4 mmol) was added. The ethanolamine derivative of 9-BBN then precipitated out and was washed successively with pentanes. The pentane layers were decanted, combined and concentrated *in vacuo* to afford the title compound as a 2:1 mixture of diastereomers. The crude material was purified to afford the major diastereomer which was then taken on in the subsequent reactions. Data are for the major diastereomer. ¹H NMR (300 MHz, CDCl₃) δ 7.55 (d, *J* = 7.5 Hz, 1 H), 7.29–7.22 (m, 2

H), 7.10–7.05 (m, 1 H), 5.93–5.90 (m, 1 H), 5.81–5.77 (m, 1 H), 4.65–4.57 (m, 1 H), 3.04–2.97 (m, 1 H), 2.85–2.77 (m, 1 H), 2.61–2.39 (m, 3 H), 1.38 (m, 1 H).

2-((1S,4R)-4-(2-bromobenzyl)cyclopent-2-enyl)ethanol (IV-191).⁴⁹ A flame-dried flask was charged with 5-(2-bromobenzyl)cyclopent-2-enol (251 mg, 0.991 mmol), triethylorthoacetate (6.11 g, 5.43 mL, 29.75 mmol) and propionic acid (7.1 μ L, 0.089 mmol), equipped with a reflux condenser and heated to 140 °C overnight until the starting material was consumed as judged by ¹H NMR of an aliquot of the reaction mixture. The reaction mixture was cooled to rt, transferred to an Erlenmeyer flask and diluted with THF, and 1M HCl was added and the reaction was stirred for several hours. The crude product was extracted with diethyl ether (3 X 100 mL), washed with NaHCO₃, dried over Na₂SO₄, and concentrated *in vacuo*. The material was then used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.53 (d, *J* = 7.6 Hz, 1 H), 7.24–7.18 (m, 2 H), 7.08–7.04 (m, 1 H), 5.72–5.68 (m, 2 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 3.19–3.13 (m, 2 H), 2.82–2.70 (m, 2 H), 2.37–2.24 (m, 2 H), 1.90–1.83 (m, 1 H), 1.69–1.62 (m, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

2-(4-(2-bromobenzyl)cyclopent-2-enyl)ethanol (IV-192). A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and was charged with 2-((1S,4R)-4-(2-bromobenzyl)cyclopent-2-enyl)ethanol (319 mg, 0.987 mmol) and diethyl ether (3 mL). The reaction mixture was cooled to 0 °C, and a solution of LiAlH₄ (3 mL, 3.04 mmol, 1 M in diethyl ether) was added dropwise, and the reaction mixture was warmed to room temperature and stirred for 8 h. The reaction mixture was then cooled to 0 °C and water (1 mL) was added dropwise followed by 10 M NaOH (2 mL) and additional water (3 mL). The resulting mixture was decanted, dried over anhydrous

sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography using ethyl acetate/hexanes as the eluant to afford 113 mg (41% over two steps) of the title compound as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 7.56–7.52 (m, 1 H), 7.30–7.16 (m, 2 H), 7.10–7.03 (m, 1 H), 5.75–5.64 (m, 2 H), 3.71–3.59 (m, 2 H), 3.13–3.07 (m, 1H), 3.04–2.80 (m, 2 H), 2.77–2.73 (m, 2H), 1.85–1.50 (m, 4H).

Benzodecahydropentaleno[1,2-b]furan (IV-193). The cyclization of **IV-192** (56 mg, 0.199 mmol) following the general procedure using $\text{PCy}_3\cdot\text{HBF}_4$ as ligand afforded 21 mg (53%) of the title compound as a colorless oil. This compound was judged to be a >20:1 mixture of diastereomers by ^1H NMR analysis analysis. ^1H NMR (400 MHz, CDCl_3) δ 7.32–7.28 (m, 1 H), 7.22–7.15 (m, 3 H), 4.57 (d, $J = 6.4$ Hz, 1 H), 3.98–3.93 (m, 1 H), 3.76–3.70 (m, 1 H), 3.64 (d, $J = 7.2$ Hz, 1 H), 3.14–3.01 (m, 2 H), 2.66 (d, $J = 14.8$ Hz, 2 H), 2.10–2.02 (m, 1 H), 1.86–1.80 (m, 1 H), 1.69–1.61 (m, 1 H), 1.55–1.48 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.8, 143.3, 127.0, 126.7, 125.4, 125.2, 90.9, 68.5, 58.5, 43.9, 42.2, 38.9, 38.4, 33.8; IR (film) 2933, 2848 cm^{-1} . MS (EI) 200.1199 (200.1201 calcd for $\text{C}_{14}\text{H}_{16}\text{O}$).

References

¹ Reproduced in part with permission from “Intramolecular Pd-Catalyzed Carboetherification and Carboamination. Influence of Catalyst Structure on Reaction Mechanism and Product Stereochemistry” Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893–2901. Copyright 2006 American Chemical Society.

² Pyrrolidines: (a) Ney, J. E.; Wolfe, J. P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3605–3608. (b) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644–8651. (c) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447–6459. Tetrahydrofurans: (d) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620–1621. (E) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099–3107. (f) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468–16476. (g) Hay, M. B.; Wolfe, J. P. *Tetrahedron Lett.* **2006**, *47*, 2793–2796.

³ For intramolecular Wacker-type anti-addition reactions of alkynes bearing an alkyl(bromoaryl) group tethered to one end and an alkyl carboxylic acid to the other, see: (a) Cavicchioli, M.; Bouyssi, D.; Gore, J.; Balme, G. *Tetrahedron Lett.* **1996**, *37*, 1429–1432. (b) Bouyssi, D.; Balme, G. *Synlett* **2001**, 1191–1193.

⁴ At the time this chemistry was ongoing, reactions of *N*-aryl protected γ -amino internal olefins were limited. Since then, Boc-protected γ -amino internal olefins have been shown to undergo cyclization to afford the pyrrolidine in good yield: Bertrand, M. B.; Neukom, J. D.; Wolfe, J. P. *Manuscript in Preparation*.

⁵ Both the intermolecular and intramolecular carboetherification/carboamination reactions have an intramolecular component, as the heteroatom is tethered to the alkene in both cases. In this thesis, the term “intermolecular carboetherification/carboamination” is used to describe the reaction between an aryl bromide and a γ -unsaturated alcohol/amine that is not tethered, whereas the term “intramolecular carboetherification/carboamination” describes reactions in which the γ -unsaturated alcohol/amine is tethered to the aryl bromide.

⁶ Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055–4082. .

⁷ Beletskaya, I. P.; Bessmertnykh, A. G.; Averin, A. D.; Denat, F.; Guillard, R. *Eur. J. Org. Chem.* **2005**, 281–305 and references therein.

⁸ In our previous studies, we have noted that the large majority of products formed in intermolecular carboetherification and carboamination reactions of internal alkenes derive from syn-insertion of the alkene into the Pd-heteroatom bond of intermediate Pd(Ar)(OR) or Pd(Ar)(NRR') complexes.

⁹ (a) Through a series of deuterium labeling studies, Hayashi and co-workers have demonstrated that the Pd(II)-catalyzed oxidative cyclization of an *o*-allylphenol derivative proceeds via anti-alkoxypalladation in the presence of LiCl, and via syn-alkoxypalladation in the absence of LiCl. However, one of the stereocenters formed in

these transformations is destroyed by the β -hydride elimination step that terminates the catalytic cycle. Thus, in the absence of labeled substrates, both transformations would provide identical products. See: Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036–3037. (b) Stoltz and co-workers have recently described experiments analogous to Hayashi et al.'s deuterium labeling studies that provide further evidence for an accessible syn-oxypalladation pathway in Wacker-type cyclizations of unsaturated alcohol derivatives. See: Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778–17788. (c) For additional studies on the effect of chloride ion concentration on the mechanistic/stereochemical pathway of the Wacker oxidation, see: Hamed, O.; Thompson, C.; Henry, P. M. *J. Org. Chem.* **1997**, *62*, 7082–7083 and references therein.

¹⁰ Previously described Wacker-type cyclizations of alkenes bearing tethered heteroatoms that afford tetrahydrofuran or pyrrolidine products generally proceed via a Pd(II)-Pd(0) catalytic cycle. The mechanism of these transformations involves complexation of the alkene to Pd(II) followed by nucleophilic attack of the tethered heteroatom and β -hydride elimination to generate the heterocyclic product. The resulting Pd(H)(X) complex undergoes reductive elimination of HX to provide a Pd(0) complex, which is then reoxidized to Pd(II) by an added oxidant. Catalysts employed for these reactions generally contain halide, carboxylate, or amine ligands rather than phosphine ligands. For further details, see: (a) Reference 14. (b) Semmelhack, M. F.; Bodurov, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496–1498. (c) Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1997**, *62*, 2113–2122.

¹¹ For examples of heterocycles bearing attached heterocycles and heterocycles bearing attached carbocycles, see: (a) Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269–303. (b) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407–2474. (c) Hoppe, R.; Scharf, H.-D. *Synthesis* **1995**, 1447–1464. (d) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 298–300. (e) Ukiya, M.; Akihisa, T.; Yasukawa, K.; Kasahara, Y.; Kimura, Y.; Koike, K.; Nikaido, T.; Takido, M. *J. Agric. Food Chem.* **2001**, *49*, 3187–3197. (f) Spinella, A.; Mollo, E.; Trivellone, E.; Cimino, G. *Tetrahedron* **1997**, *53*, 16891–16896. (g) Rasmusson, G. H.; Reynolds, G. F.; Steinberg, N. G.; Walton, E.; Patel, G. F.; Liang, T.; Cascieri, M. A.; Cheung, A. H.; Brooks, J. R.; Berman, C. *J. Med. Chem.* **1986**, *29*, 2298–2315. (g) Arthur, H. R.; Ko, P. D. S. *Phytochemistry* **1974**, *13*, 2551–2557. For representative examples of other strategies that generate attached rings via C-C bond-forming reactions between cyclic precursors, see: (h) Lemieux, R. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1998**, *120*, 5453–5457. (i) Lebsack, A. D.; Overman, L. E.; Valentekovich, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 4851–4852.

¹² Spinella, A.; Mollo, E.; Trivellone, E.; Cimino, G. *Tetrahedron* **1997**, *53*, 16891–16896.

¹³ Morita, H.; Takatsu, H.; Shen, Y.-C.; Kobayashi, J. *Tetrahedron Lett.* **2004**, *45*, 901–904.

- ¹⁴ Takikawa, H.; Yoshida, M.; Mori, K. *Tetrahedron Lett.* **2001**, *42*, 1527–1530.
- ¹⁵ Kodama has also employed an ene reaction in the preparation of the carbocyclic ring, see: Hioki, H.; Hamano, M.; Kubo, M.; Uno, T.; Kodama, M. *Chem. Lett.* **2001**, 898–899.
- ¹⁶ Bruyere, D.; Bouyssi, D.; Balme, G. *Tetrahedron* **2004**, *60*, 4007–4017.
- ¹⁷ Jeffrey, T. *Tetrahedron Lett.* **1991**, *32*, 2121–2124.
- ¹⁸ Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.
- ¹⁹ Further optimization experiments revealed that use of bases such as triethylamine and potassium carbonate did not afford the desired cyclization products.
- ²⁰ Aldehyde products derived from oxidation of the primary alcohol moiety were not observed, but it is likely that these side products are not stable under the reaction conditions.
- ²¹ Basic trialkylphosphine ligands such as tricyclohexylphosphine and trimethylphosphine were employed in the form of their air-stable tetrafluoroborate salts. These ligands (and all other reagents employed in these reactions) were weighed and handled in air. See: Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295–4298.
- ²² The products were isolated in 40% yield as a 17:2:1:1 mixture of diastereomers. However, analysis of the crude reaction mixture indicated that the diastereomers were formed in a 9:2:1:1 ratio, suggesting that partial resolution of the diastereomers occurred upon chromatographic purification.
- ²³ γ -(*N*-Boc-amino) alkenes have been shown to undergo intermolecular carboamination reactions to provide pyrrolidine products, see reference 2c.
- ²⁴ For examples of transannular alkene insertion reactions of intermediates bearing exocyclic alkylpalladium moieties and/or exocyclic alkenes, see: (a) Link, J. T. *Org. React.* **2002**, *60*, 157–534. For representative examples, see: (b) Hulin, B.; Newton, L. S.; Cabral, S.; Walker, A. J.; Bordner, J. *Org. Lett.* **2004**, *6*, 4343–4345. (c) Fox, M. E.; Li, C.; Marino, J. P., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467–5480.
- ²⁵ For studies on the formation of Pd(Ar)(OR) and Pd(Ar)(NR₂) complexes, see: (a) Yamashita, M.; Cuevas Vicario, J. V.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 16347–16360 and references therein. (b) Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504–6511 and references therein.
- ²⁶ No examples of sp³ C–O bond-forming reductive elimination from Pd(II) complexes have been previously described. One transformation that may involve sp³ C–N bond-forming reductive elimination from a Pd(II) complex with no syn- β -hydrogen atoms has been described by Stahl and co-workers. See: (a) Brice, J. L.; Harang, J. E.; Timokhin, V.

I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868–2869. For examples of related sp^3 carbon-heteroatom bond-forming reductive elimination from Pd(IV), Pt(IV), and Ni(III), see: (b) Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890–2891 and references therein. (c) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542–9543. (d) Williams, B. S.; Goldberg, K. I. *J. Am. Chem. Soc.* **2001**, *123*, 2576–2587. (E) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2180–2192.

²⁷ Although related sp^2C-O bond-forming reductive elimination is well established, reductive elimination in aryl sp^2 systems has been demonstrated to proceed via an addition/elimination mechanism similar to nucleophilic aromatic substitution, which is not an accessible pathway for reductive elimination to form sp^3C-O bonds. For details, see ref 19b.

²⁸ For lead references on reversible carbopalladation, see: (a) Campora, J.; Gutierrez-Puebla, E.; Lopez, J. A.; Monge, A.; Palma, P.; del Rio, D.; Carmona, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 3641–3644. (b) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119–122.

²⁹ (a) Bartolome, C.; Espinet, P.; Martin-Alvarez, J. M.; Villafane, F. *Eur. J. Inorg. Chem.* **2004**, 2326–2337. (b) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598–11599.

³⁰ (a) Villanueva, L. A.; Abboud, K. A.; Boncella, J. M. *Organometallics* **1992**, *11*, 2963–2965. (b) Bryndza, H. E. *Organometallics* **1985**, *4*, 406–408.

³¹ For other recent examples of syn-alkene insertion into late transition metal-heteroatom bonds, see: (a) Helaja, J.; Gottlich, R. *J. Chem. Soc., Chem. Commun.* **2002**, 720–721. (b) Tsutsui, H.; Narasaka, K. *Chem. Lett.* **1999**, 45–46. (c) Reference 14a.

³² Yeh, M.-C. P.; Tsao, W.-C.; Tu, L.-H. *Organometallics* **2005**, *24*, 5909–5915.

³³ Wacker-type carbonylative carboetherifications described by Semmelhack and Bodurow afford products resulting from anti-addition of an oxygen atom and an ester group across an alkene.

³⁴ (a) Reference 20. (b) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496–1498. (c) Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1997**, *62*, 2113–2122.

³⁵ Gibson, S. E.; Guillo, N.; Middleton, R. J.; Thuilliez, A.; Tozer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 447–456 and references therein.

³⁶ Dosen-Micovic, L.; Lorenc, L.; Mihailovic, M. L. *Tetrahedron* **1990**, *46*, 3659–3666.

³⁷ (a) Hoffmann, R. W. *Chem. Rev.* **1989**, 89, 1841–1860. (b) Hart, D. J. *J. Am. Chem. Soc.* **1980**, 102, 397–398. (c) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, 110, 1547–1557.

³⁸ As noted above, our previously described intermolecular carboamination reactions of terminal alkenes have proceeded with high stereoselectivity for the formation of *trans*-2,5-disubstituted *N*-arylpyrrolidines, which is also consistent with favorable pseudoaxial orientation of a C-1 substituent in the absence of medium-ring transannular interactions. However, the effects of *E/Z*-alkene geometry on the ratio of *trans/cis*-pyrrolidine pyrrolidine formation have not yet been examined in intermolecular transformations. For further details, see ref 2a.

³⁹ The addition of base has been observed to dramatically increase the rate and/or yield of oxidative Wacker cyclizations of *o*-allylphenol derivatives. See: (a) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, 42, 2892–2895. (b) Larock, R. C.; Wei, L.; Hightower, T. R. *Synlett* **1998**, 522–524.

⁴⁰ The rate and/or yield of Wacker cyclization reactions that afford tetrahydrofuran products have also been observed to decrease with increasing steric bulk at the C1 position. See: (a) Meulemans, T. M.; Kiers, N. H.; Feringa, B. L.; van Leeuwen, P. W. N. M. *Tetrahedron Lett.* **1994**, 35, 455–458. (b) Hosokawa, T.; Hirata, M.; Murahashi, S.-i.; Sonoda, A. *Tetrahedron Lett.* **1976**, 17, 1821–1824.

⁴¹ Nakhla, J. S.; Wolfe, J. P. *Unpublished Results*.

⁴² Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, 97, 5434–5447.

⁴³ Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, 52, 7525–7546.

⁴⁴ Bruyère, D.; Bouyssi, D.; Balme, G. *Tetrahedron* **2004**, 60, 4007–4017.

⁴⁵ Matikainen, J.; Kaltia, S.; Hämäläinen, M.; Hase, T. *Tetrahedron* **1997**, 53, 4531–4538.

⁴⁶ Silverstein, R.M.; Ryskiewicz, E. E.; Willard, C.; Koehler, R. C. *J. Org. Chem.* **1955**, 20, 668–672.

⁴⁷ Mino, T.; Masuda, S.; Nishio, M.; Yamashita, M. *J. Org. Chem.* **1997**, 62, 2633–2635.

⁴⁸ Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, 97, 5434–5447.

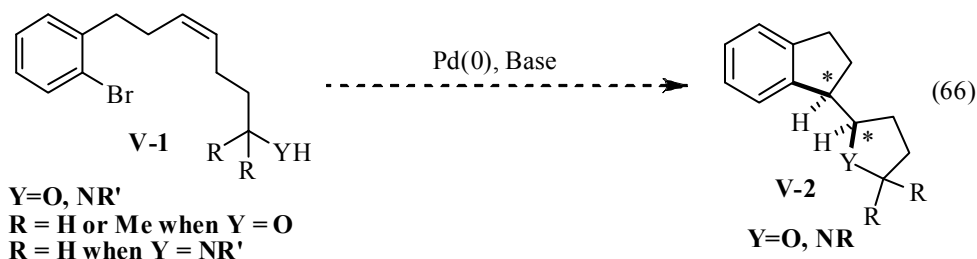
⁴⁹ (a) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1975**, 40, 1864–1865. (b) Gundersen, L.-L.; Benneche, T.; Undheim, K. *Tetrahedron Lett.* **1992**, 33, 1085–1088.

Chapter V

Stoichiometric Studies Towards the Synthesis of Likely Intermediates in Intramolecular Pd-Catalyzed Carboetherification and Carboamination Reactions¹

Introduction to Stoichiometric Study: Goals and Challenges

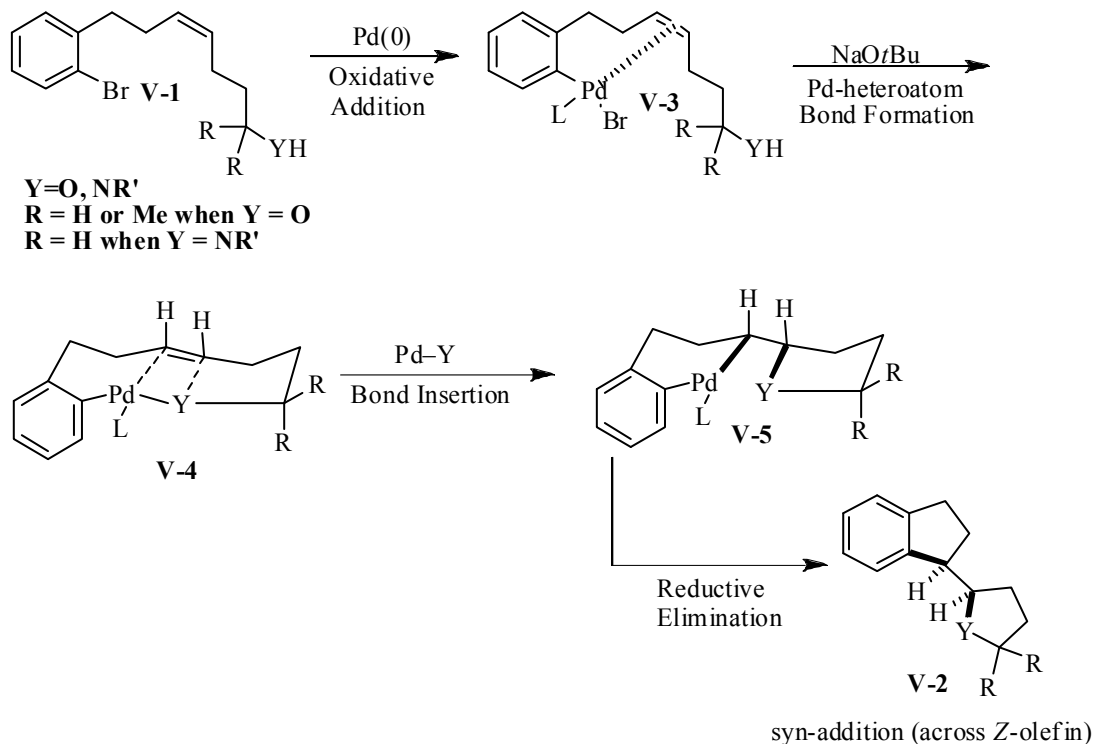
As outlined in the previous chapter, we have developed a Pd-catalyzed intramolecular carboetherification and carboamination reaction of substrates such as **V-1** (eq 66). We had observed that catalyst structure has a large impact on the stereochemical outcome of these reactions, which we attributed to a catalyst dependent change in mechanism. To further probe this hypothesis, we sought to generate and study the reactivity of some of the key intermediates in our proposed catalytic cycle.



This chapter details our preliminary investigations on stoichiometric heteropalladation reactions of **V-1**. In our first experiments, we wanted to examine stoichiometric reactions providing access to the products resulting from syn-addition across the olefin. The goals, therefore, of this project were to characterize and/or isolate oxidative addition complexes such as **V-3**, form and attempt to characterize macrocyclic

Pd-alkoxide or Pd-amido species **V-4**, and observe alkene insertion (to **V-5**) followed by reductive elimination to heterocycle **V-2**.

Scheme 74. Proposed Mechanism for Carboetherification/Carboamination Reaction Providing Products Resulting in Syn-Addition Across Olefin of Substrate **V-1**



While our goals as proposed above were well-founded, we felt that the chemistry could be challenging to carry out. We realized that it may be difficult to observe the oxidative addition complex or other proposed intermediates, and full characterization of these species (**V-3**, **V-4**, **V-5**) would only be possible upon isolation, which would require a certain degree of stability for these intermediates. Additionally, as mentioned in Chapter IV, only one previous report has described transformations that presumably involve macrocyclic palladacycles bearing both Pd–C and Pd–heteroatom bonds,² and

transannular syn-alkene insertions of macrocyclic palladacycles bearing internal olefins are unknown.

Results

Stoichiometric Reactions: Examination of Oxidative Addition

We began our study by examining substrates introduced in Chapter IV that contain an aryl halide moiety appended to an unsaturated alcohol or amine as shown in Figure 10. We sought to investigate the reactivity of these substrates with various palladium complexes that are available either commercially, or could be prepared in few steps from other palladium sources.³ Figure 11 contains a list of palladium complexes (along with the respective cone angle of the phosphine ligands) which were examined in the reactions that will be discussed in the remainder of this chapter.

Figure 10. Substrates Used in Stoichiometric Investigation

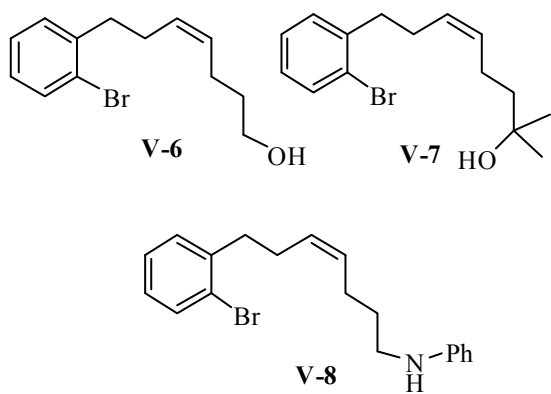
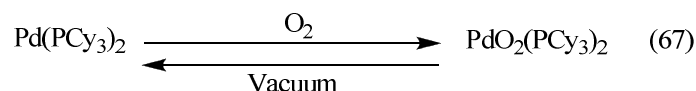


Figure 11. Catalysts Used in Stoichiometric Investigation

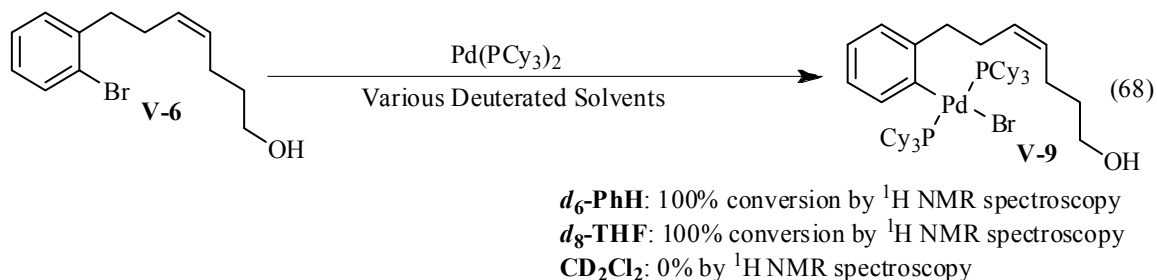
Complex	Cone Angle of Phosphine Ligand
Pd(PCy ₃) ₂	170
Pd[P(<i>t</i> -BuCy ₂) ₂] ₂	174
Pd[P(<i>t</i> -Bu) ₂ Cy] ₂	178
Pd[P(<i>t</i> -Bu) ₃] ₂	182
Pd[P(<i>o</i> -tol) ₃] ₂	194

Our initial experiments focused on reaction of *Z*-alkene **V-6**, which contains a pendant primary alcohol. This substrate was chosen due to its reactivity in the catalytic reaction with Pd₂(dba)₃/PCy₃·HBF₄ and the ready availability of Pd(PCy₃)₂. However, the use of commercially available Pd(PCy₃)₂ was initially complicated by the presence of an impurity in the Pd-complex. Certain batches of Pd(PCy₃)₂ were green in color, whereas the pure complex is known to be a white solid. In addition, ³¹P NMR analysis of this material showed the presence of an extra peak at δ 45.60 ppm; the chemical shift of pure Pd(PCy₃)₂ is δ 39.60 ppm. After a thorough search of the literature, it was discovered that binding of O₂ to the metal produces a green-colored complex (eq 67). However, the authors did not publish the ³¹P NMR spectral data for the O₂-bound complex.⁴ The binding of O₂ to Pd(PCy₃)₂ is known to be reversible. Therefore, this impurity could be removed simply by placing the complex under vacuum in the glovebox for several minutes. If the green color did not completely dissipate, the complex was

dissolved in the solvent to be used for a given experiment. Removal of the solvent under vacuum in the glovebox then provided pure Pd(PCy₃)₂.

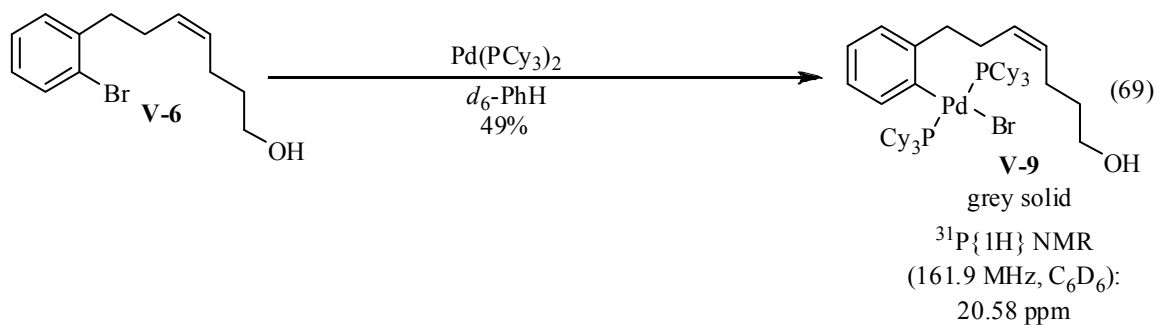


With pure substrates in hand, we found that treatment of **V-6** with Pd(PCy₃)₂ at 25°C in *d*₆-benzene or *d*₈-THF led to clean conversion to Pd^{II}-oxidative addition complex **V-9** (eq 68). However, only starting material was observed in the attempted oxidative addition of **V-6** to Pd(PCy₃)₂ when CD₂Cl₂ was used as the solvent.

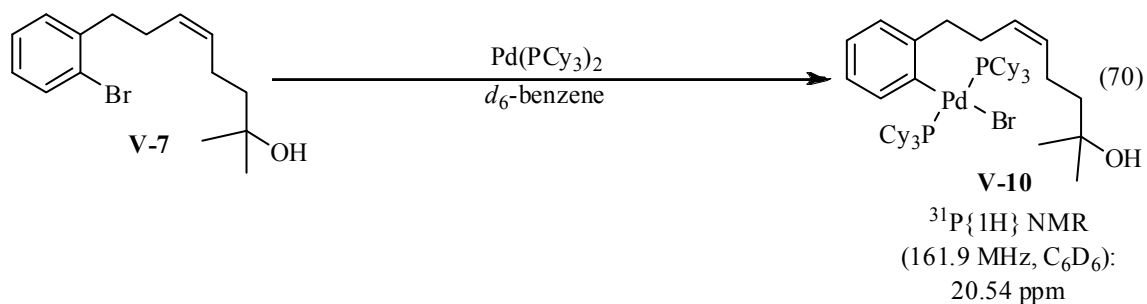


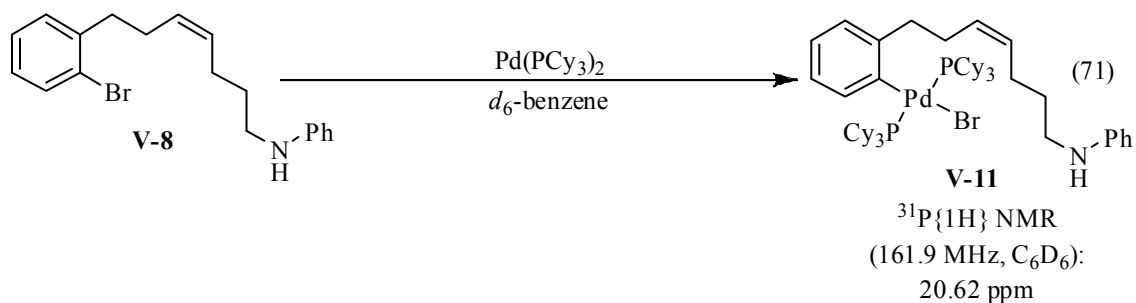
The synthesis of **V-9** on a preparative scale was accomplished by treatment of 2.0 eq (80.3 mg) of **V-6** with 1.0 eq (100 mg) of Pd(PCy₃)₂ in 14 mL of anhydrous benzene in a Schlenk flask for 12 h. After the benzene solvent was removed, a 3:1 mixture of pentanes: diethyl ether was added and the flask was placed in the glove box freezer for 2 h. Filtration afforded 68 mg (49%) of the oxidative addition complex as a grey solid. Analysis of this material by ³¹P NMR provided a spectrum with a single peak at δ 20.58. This value is comparable to the ³¹P NMR spectra reported for Ph(Br)Pd(PCy₃)₂ (δ 20.6

ppm).⁵ Additional structural data for this compound were obtained through ¹H NMR and 2D-COSY NMR experiments. Copies of these spectra are provided in the experimental section of this thesis.



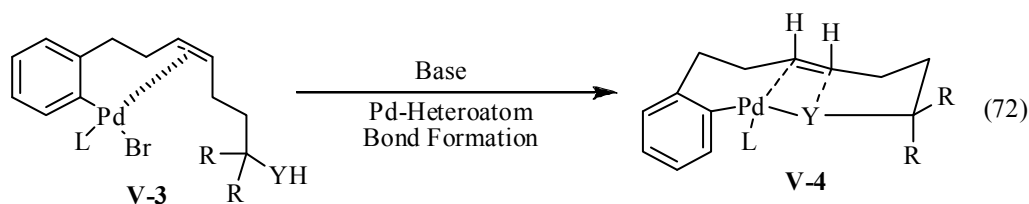
Similar oxidative addition studies were conducted with substrates **V-7** and **V-8**. Oxidative addition proceeds cleanly with Pd(PCy₃)₂ (eq 70 and 71) to afford **V-10** and **V-11**. These compounds were also characterized by ³¹P NMR (as shown below) and ¹H NMR spectroscopy.





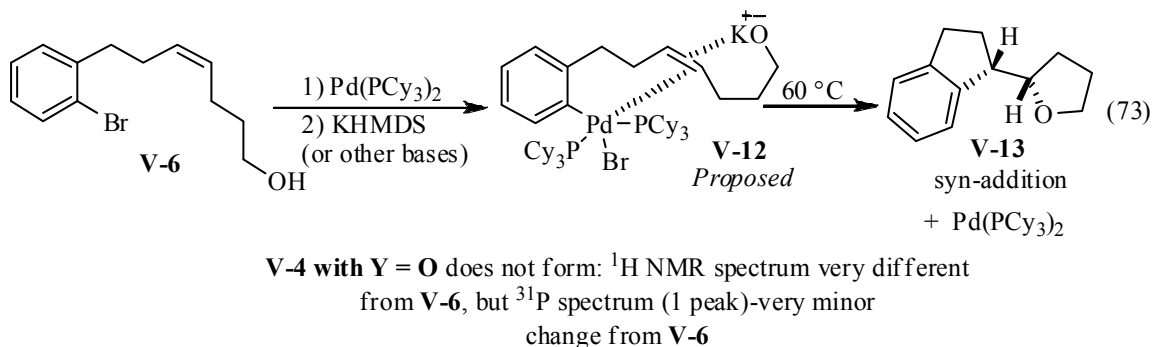
Stoichiometric Reactions: Examination of Oxypalladation/Aminopalladation

After successful preparation of oxidative addition complexes **V-9**, **V-10** and **V-11**, we sought to investigate other reaction intermediates en route to the product heterocycles **V-2**. In particular, we sought to observe palladacycle intermediate **V-4** by reaction of the oxidative addition complex **V-3** with base (eq 72).

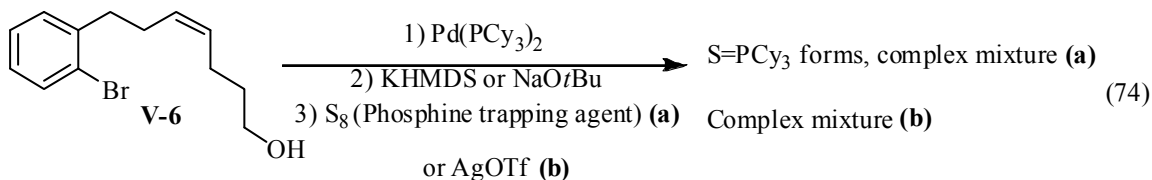


A new product was generated upon addition of base to a solution of the oxidative addition complex **V-9**, and the ^1H NMR spectrum of this new species was very different from the ^1H NMR spectrum of **V-6**. However, there were only very minor changes in the ^{31}P NMR spectrum of the molecule relative to **V-6**. In addition, free PCy_3 was not observed. Therefore, we do not currently believe we have accessed the palladacyclic intermediate analogous to **V-4** with $\text{Y} = \text{O}$. The ^{31}P NMR spectra of most $\text{L}_2\text{Pd}(\text{Ar})(\text{OR})$ complexes are shifted by 5-10 ppm relative to that of the analogous $\text{L}_2\text{Pd}(\text{Ar})(\text{Br})$ complexes.⁶ We reasoned that significant changes in the ^1H NMR coupled with minor

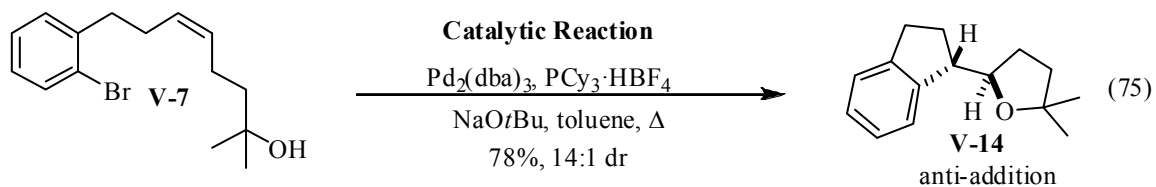
changes in the ^{31}P NMR spectrum could be a result of complexation of the activated olefin with the alkoxide species as in the proposed structure **V-12**. Efforts to drive the conversion of **V-6** to the Pd-alkoxide complex by heating (to $60\text{ }^\circ\text{C}$) instead led to immediate formation of the syn-addition product **V-13** with regeneration of $\text{Pd}(\text{PCy}_3)_2$.

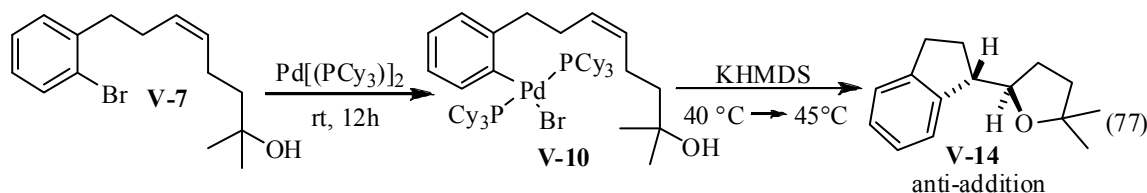
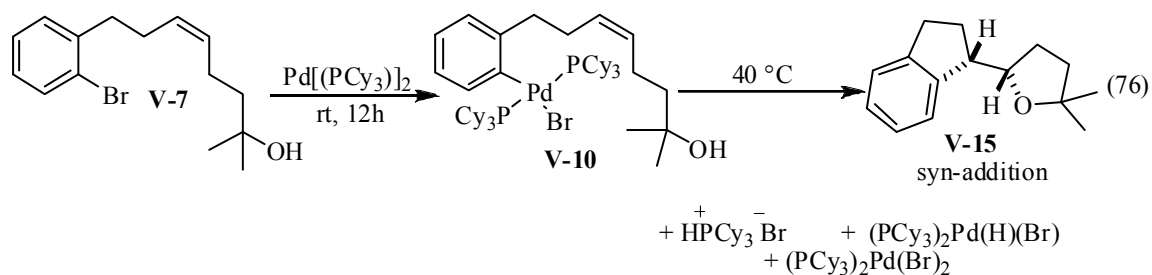


We hypothesized that perhaps we were not accessing an L_1 palladium complex containing a free site on the metal that could then form the Pd-alkoxide species quantitatively. However, attempts to facilitate phosphine disassociation from complex **V-12** via addition of sulfur as a phosphine scavenger led to the formation of complex mixtures of products; phosphine sulfide was detected (δ 62 ppm).⁷ In a separate experiment, a complex mixture of products was also formed when AgOTf was added to **V-12**.

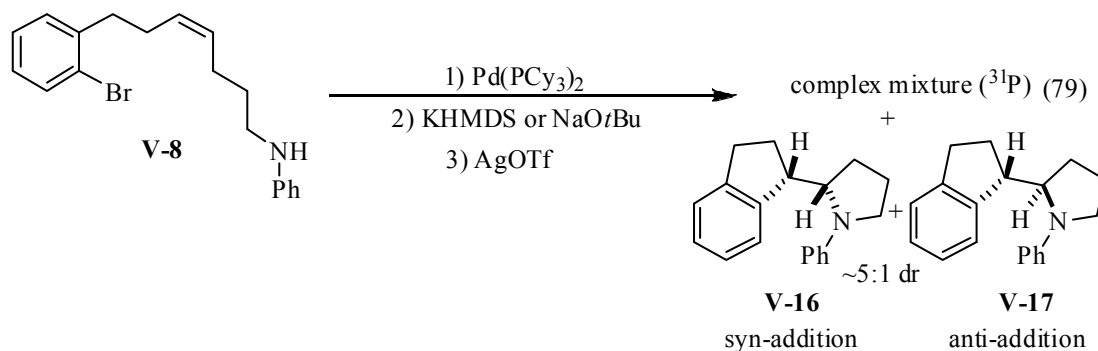
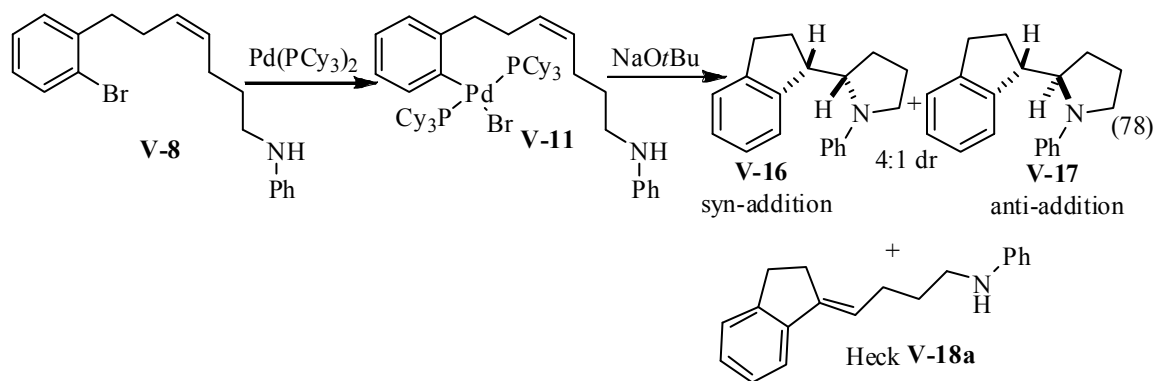


Due to our lack of success in preparing macrocycle **V-4** from primary alcohol **V-6**, we elected to examine a related tertiary alcohol substrate (**V-7**). It is worth noting (as described in Chapter IV) that the $\text{Pd}_2(\text{dba})_3/\text{PCy}_3$ -catalyzed reaction of **V-7** in the presence of NaOtBu affords anti-addition diastereomer **V-14** in 78% yield and 14:1 dr (eq 75). Treatment of tertiary alcohol **V-7** with stoichiometric $\text{Pd}(\text{PCy}_3)_2$ at room temperature led to formation of oxidative addition complex **V-10**, which was characterized by ^1H NMR and ^{31}P NMR spectroscopy. Interestingly, heating this complex to 40°C in the absence of base led to selective formation of the syn-addition product **V-15** (eq 76). On the other hand, the anti-addition diastereomer was generated upon addition of an external base (KHMDS) to the complex formed from the reaction of **V-7** with $\text{Pd}(\text{PCy}_3)_2$ (eq 77).





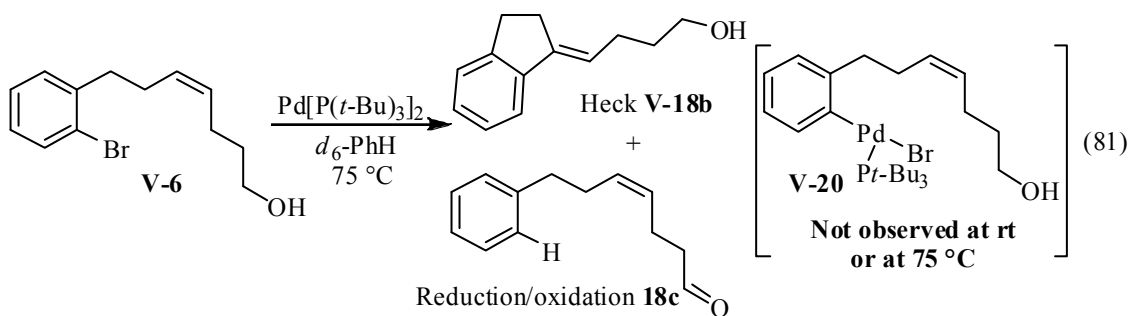
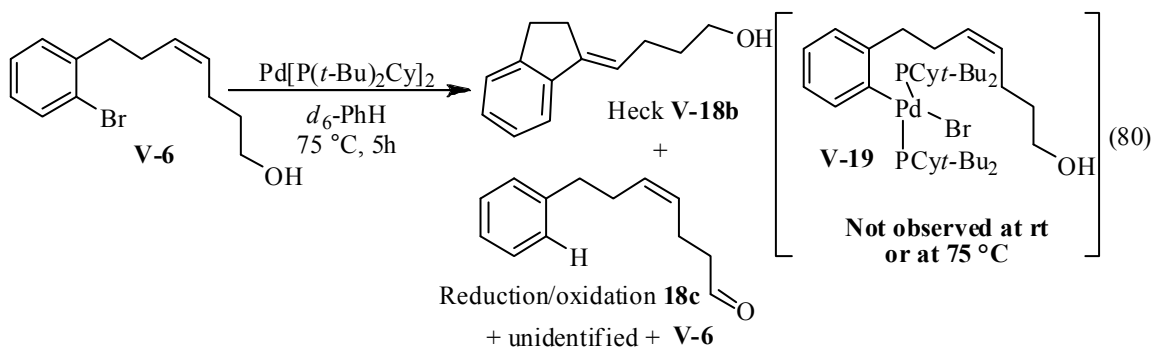
In addition to our efforts to prepare macrocyclic Pd(Ar)(OR) complexes with PCy₃ ligands, we also examined the preparation of analogous Pd(Ar)(NRR') complexes as shown below in eq 78. Treatment of **V-8** with Pd(PCy₃)₂ led to formation of oxidative addition complex **V-11**, which was characterized by ¹H NMR and ³¹P NMR spectroscopy (peak at δ 20.62 ppm in ³¹P NMR). However, when NaOtBu was added to **V-8**, syn- and anti-addition pyrrolidines **V-16** and **V-17** immediately began forming at room temperature.⁸ In addition, Heck product **V-18** was also observed in the ¹H NMR. When the experiment was repeated but with addition of AgOTf as a halide scavenger (eq 79), formation of syn- and anti-addition pyrrolidines **V-16** and **V-17**, was observed by ¹H NMR analysis, and a complex mixture of phosphine-containing species was observed by ³¹P NMR spectroscopy.



Oxidative Addition and Oxypalladation/Aminopalladation Investigation with Other Complexes

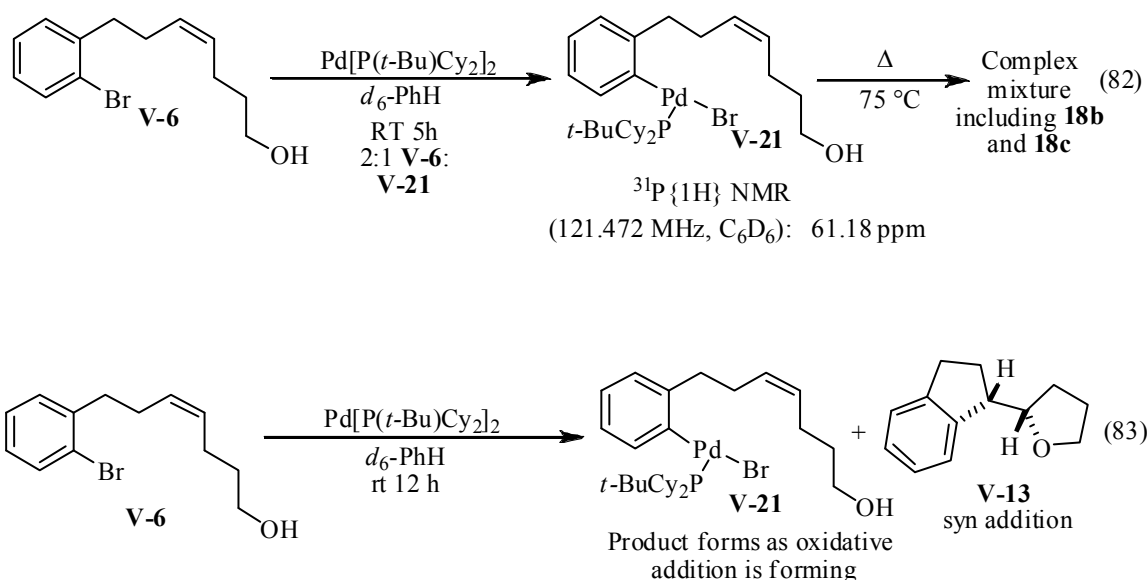
Due to the stability of complex **V-9**, we hypothesized that we may more easily arrive at a detectable Pd-alkoxide species if we could access an L_1Pd complex. Therefore other bulky metal complexes were utilized in this effort, such as $\text{Pd}[\text{P}(t\text{-Bu})_2\text{Cy}]_2$. However, the use of $\text{Pd}[\text{P}(t\text{-Bu})_2\text{Cy}]_2$ did not lead to any detectable quantity of the oxidative addition complex **V-19** at room temperature or with heating. Rather, heating **V-6** led to the formation of Heck side product **V-18b**, oxidation product **18c**, as well as unidentified product(s) and recovered starting material. Similarly, treatment of **V-6** with stoichiometric $\text{Pd}[\text{P}(t\text{-Bu})_3]_2$ did not lead to any detectable amount of oxidative addition

complex **V-20**, and heating to 75 °C to help initiate oxidative addition led to formation of Heck product **V-18b** as well as products resulting from oxidation of the starting material **18c**.



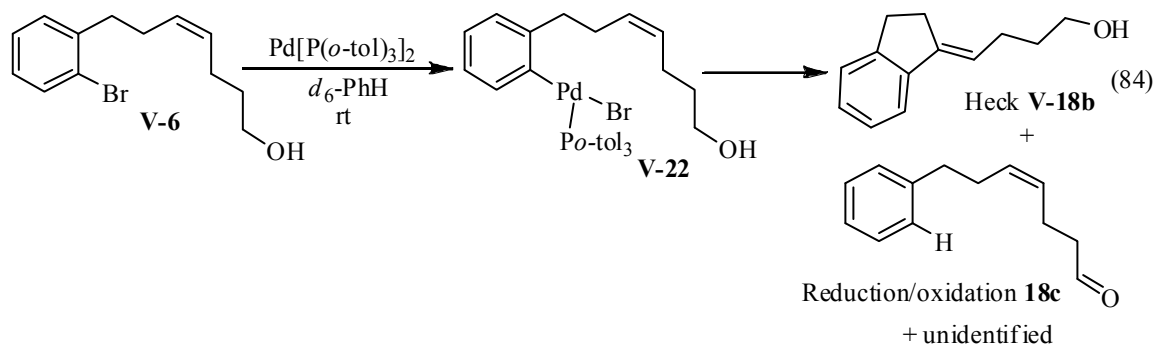
Other attempts to arrive at an L_1Pd complex with palladium complexes composed of electron-rich monodentate phosphine ligands were also investigated. Use of $\text{Pd}[\text{P}(t\text{-Bu})\text{Cy}_2]_2$ with **V-6** led to slow conversion (~6-8 h) to the oxidative addition complex **V-21** (2:1 ratio of **V-6**: **V-21** at 6-8 h). Analysis of this material by ^{31}P NMR provided a spectrum with a peak at δ 61.18. This value is comparable to the ^{31}P NMR spectra reported for the aryl palladium iodide dimer $\text{Ph}(\text{I})\text{Pd}(\text{P}t\text{-Bu}_2\text{Cy})$ (δ 64.4 ppm).⁹ Additionally, a broad peak was observed in ^{31}P NMR at δ 27.6 ppm which indicated the

presence of free phosphine. Additional structural data for this compound were obtained through ^1H NMR spectroscopy. It is evident that complex **V-21** is monoligated since the $\text{Ph(I)Pd(P}t\text{-BuCy}_2)_2$ complex is reported to have a ^{31}P chemical shift of δ 32.6 ppm. Heating the mixture of **V-6** and **V-21** in hopes of driving the quantitative formation to the oxidative addition complex **V-21** or to the palladium alkoxide (e. g. **V-4**, $\text{Y} = \text{O}$) led to complex mixtures of products. When the experiment was repeated (**V-6** \rightarrow **V-21**) and left at room temperature for 12 hours, cyclization to syn-addition product **V-13** occurred concurrently (experiment was monitored over 12 h period and no intermediates were observed other than those noted above).

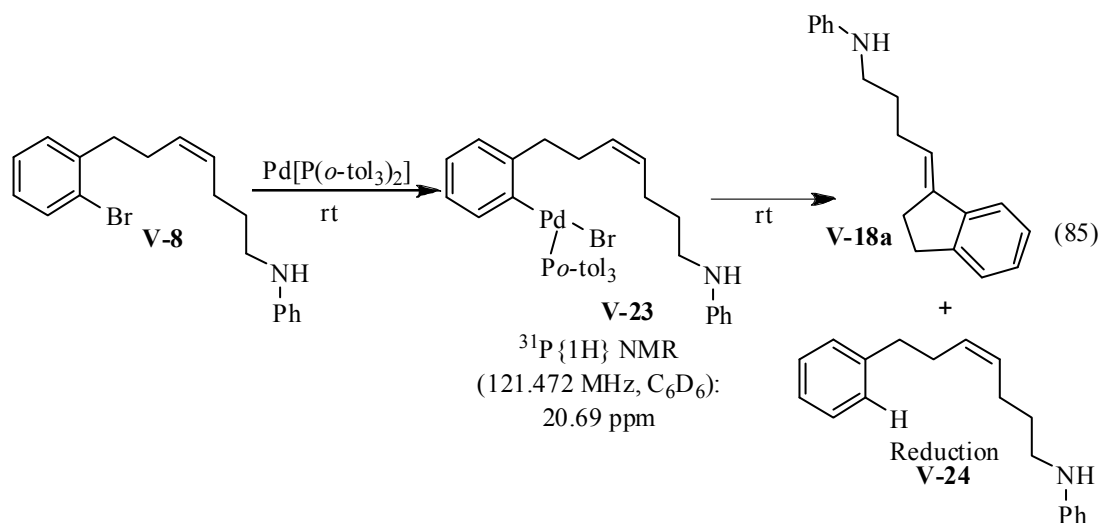


Reaction of **V-6** with stoichiometric $\text{Pd}[\text{P}(o\text{-tol})_3]_2$ without the addition of base at rt (eq 84) led to the monoligated oxidative addition species **V-22**. Analysis of this material by ^{31}P NMR provided a spectrum with a peak at δ 20.29. This value is comparable to the ^{31}P NMR spectra reported for other aryl palladium halide complexes

ligated to $P(o\text{-tol})_3$ (e.g. δ 28.5 ppm).¹⁰ Additionally, free phosphine was observed in the ^{31}P NMR at δ -29.09 ppm. Additional structural data for this compound were obtained through ^1H NMR spectroscopy. However, Heck cyclization afforded product **V-18** rather than the desired tetrahydrofuran **V-13**. In conclusion, in cases where $L_1\text{Pd}$ complexes could be generated, other side reactions occur faster than the desired transformation.



Attempts to prepare $L_1\text{PdAr}(\text{NRR}')_2$ complexes with bulky ligands were also unsuccessful. An $L_1\text{Pd}$ complex was also generated (**V-23**) with **V-8** and $\text{Pd}[P(o\text{-tol})_3]_2$ but this lead primarily to the Heck product **V-18a** and reduction of starting material **V-24**. Analysis of the reaction mixture indicated a peak in the ^{31}P NMR spectrum at δ 20.69 ppm, corresponding to the oxidative addition species **V-23**. This value is comparable to the ^{31}P NMR spectra reported for other monoligated $P(o\text{-tol})_3$ oxidative addition complexes as already discussed above.¹⁰ Additionally, free phosphine was observed in the ^{31}P NMR spectrum at δ -29.09 ppm, further supporting the formation of the monoligated species **V-23**.



Discussion

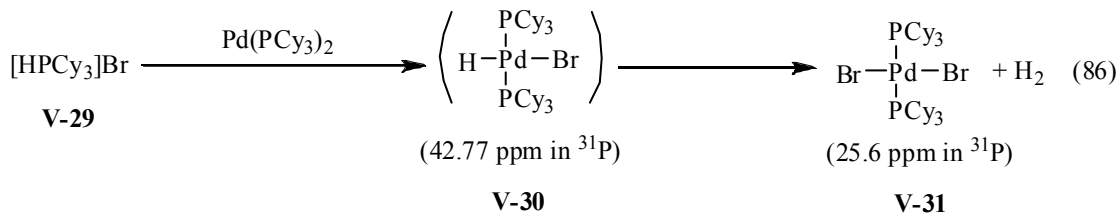
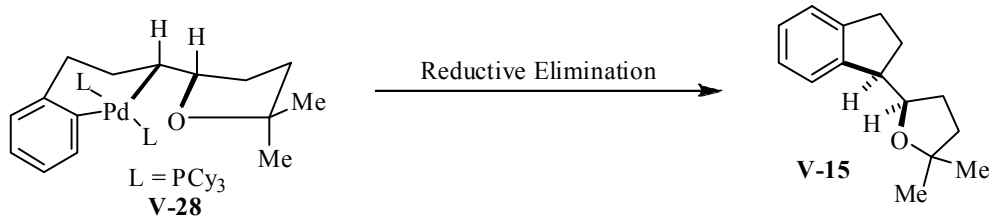
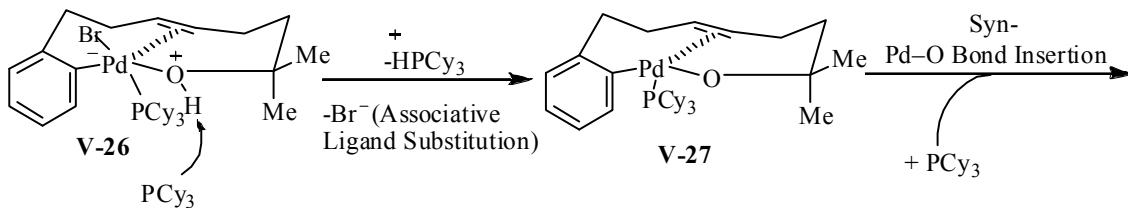
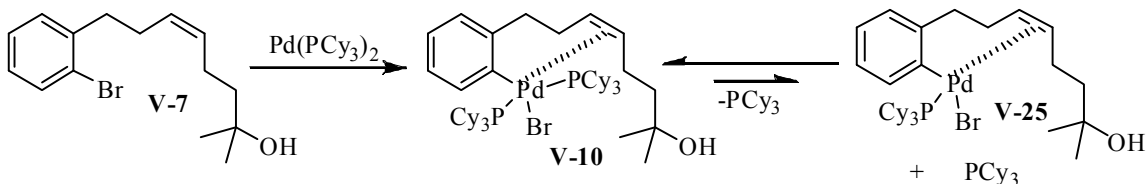
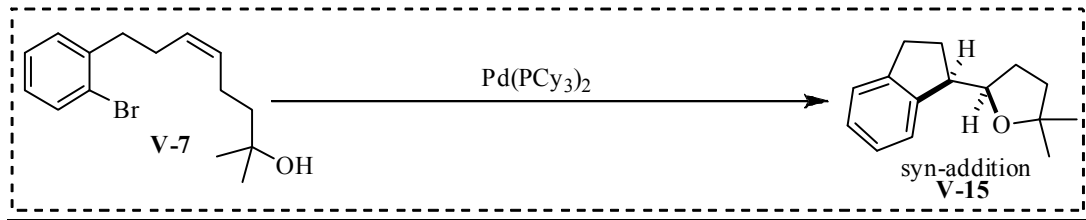
The oxidative addition of substrates **V-6**, **V-7**, and **V-8** to $\text{Pd}(\text{PCy}_3)_2$ provides stable complexes such as **V-9**, which are isolable $(\text{PCy}_3)_2\text{Pd}(\text{Ar})(\text{X})$ complexes bearing pendant alcohols. Surprisingly, intramolecular carbopalladation of this complex was not observed, which adds further support to the hypothesis that alkene insertion into Pd–O or Pd–N bonds is faster than alkene insertion into Pd–Ar bonds (Chapter IV, Schemes 63 and 64). The fact that two PCy_3 ligands are bound to **V-9** likely contributes to the stability of the complex, which presumably facilitates isolation but slows the rate of Pd–O bond formation. Use of bulkier ligands that may affect generation of analogous L_1Pd complexes has not yet led to isolable derivatives.

Interestingly, syn addition across the *Z*-olefin of substrate **V-6** and **V-7** is observed when no external base is added to the reaction. It is likely that the syn-addition products discussed in eq 76 and 77 (shown below for 3° alcohol substrate **V-7**) is generated through a mechanism involving a Pd-macrocycle as proposed in Chapter IV. Oxidative addition of the $\text{Pd}(\text{PCy}_3)_2$ to **V-9** affords oxidative addition complex **V-10**. It is

likely that due to the pKa differences between $^+\text{HPCy}_3$ (pKa = 9.7) and the alcohol (pKa = 16-17), that deprotonation does not occur substantially without coordination of the alcohol to the metal. Phosphine disassociation likely occurs to a non-detectable degree which would allow for the alcohol to bond to the metal and undergo deprotonation by the phosphine (as in **V-26**) to afford Pd-macrocycle **V-27**. Deprotonation of the alcohol forms $^+\text{HPCy}_3$. The formation of Br^- occurs via associative ligand substitution upon coordination of the alcohol to the metal. Reaction of this species with $\text{Pd}(\text{PCy}_3)_2$ accounts for the formation of **V-30** (eq 86). Insertion into the Pd–O bond provides palladacyclic intermediate **V-28**, which is followed by reductive elimination to provide tetrahydrofuran **V-13**, the product of syn-addition across the *Z*-olefin.

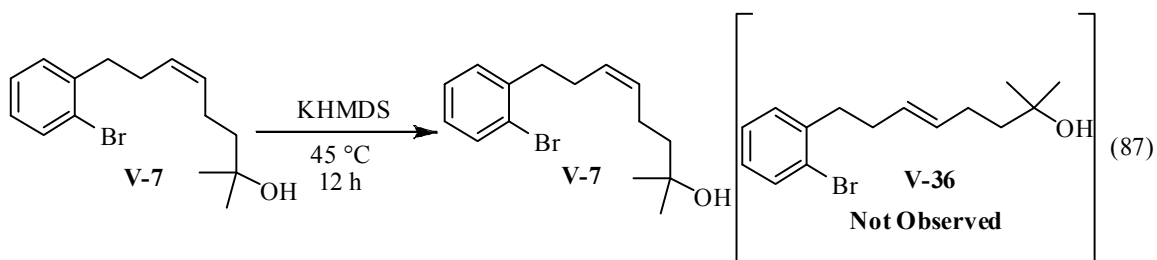
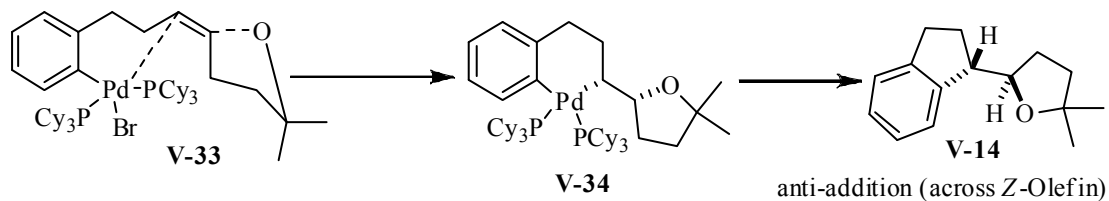
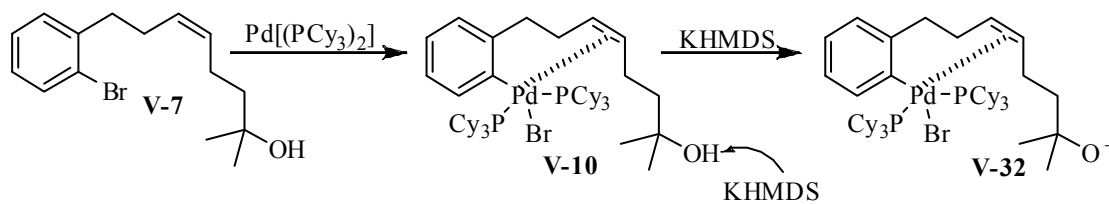
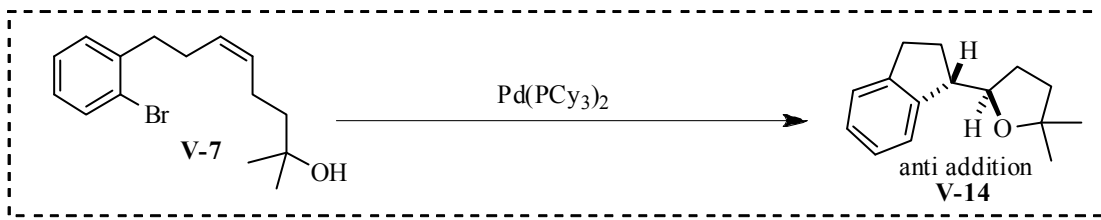
Byproducts observed in the NMR spectra which lend credence to the mechanism below include the formation of palladium hydride **V-30** characterized by both ^1H and ^{31}P NMR spectroscopy and the product of its decomposition, the dibromide **V-31** (eq 86), which was characterized by ^{31}P NMR spectroscopy.¹¹ A mechanism involving insertion of the olefin into the Pd-aryl bond of macrocycle **V-27** cannot be ruled out, but has been shown to be non-competitive in a probe experiment (see Chapter IV, Schemes 63 and 64), which indicated the rate of Pd–O bond insertion is faster with our optimal catalyst system than Pd–C bond insertion.

Scheme 75. Proposed Mechanism for Conversion of V-7 to V-15 (Syn-Addition)



The mechanism below describes what we believe to be occurring in the stoichiometric experiment using a tertiary alcohol when an external base is added, which results in anti-addition across the *Z*-olefin. Oxidative addition of the L₂Pd complex affords oxidative addition complex **V-10**. Deprotonation of the alcohol by KHMDS affords bisphosphine complex **V-32**. The deprotonated alcohol likely attacks the Pd-activated olefin to afford **V-33** which then undergoes anti-oxypalladation to afford **V-34** and upon reductive elimination, tetrahydrofuran **V-14** is generated, resulting from anti-addition across the *Z*-olefin. A possible explanation for this difference in reactivity between Scheme 75 (syn-addition) and Scheme 76 (anti-addition) may be that in the syn-addition mechanism, the alcohol is only deprotonated upon coordination of the alcohol to the metal. Therefore, once it is coordinated, the phosphine is likely in the coordination sphere and can deprotonate the alcohol and funnel the reaction towards Pd-macrocycle formation and the syn-addition product. On the other hand, the anti-addition product forms upon addition of base, which suggests that once deprotonated, an anti-mechanism is faster than phosphine disassociation and alkoxide coordination. Alternative mechanisms involving isomerization of the olefin to give the more thermodynamically stable *E*-olefin cannot be ruled out at this point. Preliminary studies were conducted to determine if the olefin was isomerizing under basic conditions in the absence of palladium. However, no isomerization was observed when **V-7** was heated with KHMDS at 45 °C in toluene overnight. Nonetheless, we cannot rule out isomerization via reversible Pd-mediated C-H bond activation at this point.

Scheme 76. Proposed Mechanism for Conversion of V-7 to V-14 (Anti-Addition)



Conclusion

The stoichiometric experiments discussed in this chapter suggest that oxidative addition is rate limiting, at least in many of the systems examined in this chapter. In addition, since most substitutions at square planar Pd(II) proceed by an associative mechanism, it is imperative that we arrive at the monoligated Pd-species in order to observe the intermediate palladacycle **V-4**. The results in this chapter suggest that the phosphine is slowly disassociating from the metal to a non-detectable amount allowing for nucleophilic attack on the metal by the heteroatom, displacement of Br⁻, reassociation of the phosphine, and funneling to the syn-addition product. The results obtained with an external base as in Scheme 76 suggest that we can control the mechanism by which the reaction proceeds under stoichiometric conditions as well with the same complex. When the phosphine behaves as the base, one accesses the syn-addition pathway as in Scheme 75; on the other hand, when an external base such as KHMDS is added after formation of the oxidative addition complex, the anti-product forms as in Scheme 76.

The characterization and analysis of intermediates discussed in this chapter is a worthwhile challenge and will likely lead to interesting results. Future work on this project will include full isolation and characterization of the oxidative addition species discussed in this chapter and Chapter IV. Additionally, it will be necessary to determine the source of the anti-addition product in Scheme 76. The results of other substrates such as **V-6** under conditions which provided both the syn and anti diastereomer in the 3° alcohol case will need to be investigated. Additional attempts to prepare L₁Pd complexes with various alcohol and amine substrates bearing tethered aryl bromides that do not generate other side products will likely be a challenge in this chemistry but results in this

chapter suggest this may be possible. Attempting this investigation at lower temperature by Variable Temperature (VT) NMR (such as, the experiment in eq 82 with Pd[(P(*t*-Bu)Cy₂)₂]) will likely be a necessary tool in accessing the elusive intermediates and is sure to generate an interesting study in the uncharted territory of Pd-macrocyclic intermediates and rates of Pd–C versus Pd-heteroatom bond insertion in palladium chemistry.

Experimental

General Considerations. All reactions were carried out under an argon or nitrogen atmosphere in oven- or flame-dried glassware. All reagents were purchased from commercial sources and were used as obtained unless otherwise noted. Pd(PCy₃)₂ was purchased from Strem Chemical Co. and used after pumping on in the glove box and other complexes were synthesized according to literature procedures (Pd[(P(*t*-Bu)Cy)₂]₂, Pd[P(*t*-Bu)₂Cy]₂, Pd[P(*t*-Bu)₂Cy]₂, Pd[P(*o*-tol)₃]₂).³ Toluene, diethyl ether, THF, and methylene chloride were purified using a Glass Contour solvent purification system and deuterated solvents were used from Cambridge Isotope Effects, stored over molecular sieves, and used without further purification. The substrates and cyclized products used and formed in this chapter were initially characterized in Chapter IV and therefore full data in CDCl₃ can be found in the experimental section of that chapter. The regiochemistry of the heterocyclic products was assigned on the basis of ¹H NMR 2-D COSY experiments (Chapter IV); stereochemistry was assigned on the basis of x-ray crystallography (see Chapter IV). Ratios of diastereomers were determined by ¹H NMR. The experiments described in this chapter were done with stoichiometric metal and thus in many cases it was not possible to get full characterization data, at least in these preliminary investigations. The substrates below were initially characterized in Chapter IV, but since the experiments in this chapter were performed in C₆D₆, the NMR data of the substrates in C₆D₆ has been inserted.

Substrate Synthesis: See Chapter IV.

NMR Data (¹H for Substrates V-6, V-7, V-8 in *d*₆-Benzene).

Z-7-(2-Bromophenyl)hept-4-en-1-ol (V-6). ¹H NMR (400 MHz, *d*₆-C₆H₆) δ 7.38 (d, *J* = 8.0 Hz, 1 H), 6.90–6.86 (m, 2 H), 6.68–6.64 (m, 1 H), 5.44–5.32 (m, 2 H), 3.27 (q, *J* = 6 Hz, 2 H), 2.70 (t, *J* = 7.2 Hz, 2 H), 2.32 (q, *J* = 8.0 Hz, 2 H), 1.97 (q, *J* = 7.2 Hz, 2 H), 1.35–1.29 (m, 2 H), 0.52 (t, *J* = 5.2 Hz, 1 H).

Z-8-(2-Bromophenyl)-2-methyloct-5-en-2-ol (V-7). ¹H NMR (400 MHz, *d*₆-C₆H₆) δ 7.37 (d, *J* = 7.6 Hz, 1 H), 6.90–6.85 (m, 2 H), 6.67–6.63 (m, 1 H), 5.46–5.37 (m, 2 H), 2.71 (t, *J* = 7.2 Hz, 2 H), 2.39–2.34 (m, 2 H), 2.06–2.00 (m, 2 H), 1.26–1.22 (m, 2 H), 1.00 (s, 6 H), 0.63 (broad s, 1 H).

Z-[7-(2-Bromophenyl)hept-4-enyl]aniline (V-8). ¹H NMR (400 MHz, *d*₆-C₆H₆) δ 7.37 (d, *J* = 8.4 Hz, 1 H), 7.20–7.16 (m, 2 H), 6.90–6.85 (m, 2 H), 6.75 (t, *J* = 7.2 Hz, 1 H), 6.67–6.63 (m, 1 H), 6.47 (d, *J* = 8.4 Hz, 2 H), 5.44–5.28 (m, 2 H), 3.03 (s, 1 H), 2.75 (t, *J* = 8 Hz, 1 H), 2.68 (t, *J* = 8.0 Hz, 2 H), 2.30 (q, *J* = 8.0 Hz, 2 H), 1.88 (q, *J* = 7.2 Hz, 2 H), 1.28–1.21 (m, 2 H), 0.41 (s, 1 H).

(±)-(1*S,2*S**)-2-Indan-1-yltetrahydrofuran (V-13).** ¹H NMR (400 MHz, *d*₆-C₆H₆) δ 7.35–7.33 (m, 1 H), 7.11–7.09 (m, 3 H), 3.81–3.75 (m, 1 H), 3.74–3.68 (m, 1 H), 3.55–3.50 (m, 1 H), 3.32–3.27 (m, 1 H), 2.86–3.79 (m, 1 H), 2.74–2.61 (m, 1 H), 2.09–2.00 (m, 1 H), 1.69–1.66 (m, 1 H), 1.61–1.54 (m, 1 H), 1.50–1.41 (m, 1 H), 1.40–1.28 (m, 2 H).

(±)-(1S*,2R*)-2-Indan-1-yltetrahydrofuran (V-13b). ¹H NMR (500 MHz, *d*₆-C₆H₆) δ 7.84 (d, *J* = 7.5 Hz, 1 H), 7.18–7.10 (m, 3 H), 3.80–3.72 (m, 2 H), 3.61–3.56 (m, 1 H), 3.20 (q, *J* = 8 Hz, 1 H), 2.78–2.72 (m, 1 H), 2.70–2.64 (m, 1 H), 1.94–1.87 (m, 1 H), 1.58–1.47 (m, 3 H), 1.46–1.38 (m, 1 H), 1.28–1.21 (m, 1 H).

(±)-(1S*,5R*)-2,2-Dimethyl-5-indan-1-yltetrahydrofuran (V-14). ¹H NMR (500 MHz, *d*₆-C₆H₆) δ 7.80 (dd, *J* = 0.5, 1 Hz, 1 H), 7.17–7.11 (m, 3 H), 3.98–3.94 (m, 1 H), 3.20 (q, *J* = 7.5 Hz, 1 H), 2.80–2.75 (m, 1 H), 2.71–2.65 (m, 1 H), 2.22–2.14 (m, 1 H), 1.96–1.89 (m, 1 H), 1.66–1.62 (m, 1 H), 1.59–1.52 (m, 1 H), 1.50–1.40 (m, 3 H), 1.23 (s, 3 H), 1.19 (s, 3 H).

(±)-(1S*,5S*)-2,2-Dimethyl-5-indan-1-yltetrahydrofuran (V-15). ¹H NMR (500 MHz, *d*₆-C₆H₆) δ 7.40–7.38 (m, 1 H), 7.14–7.11 (m, 1 H), 3.97–3.93 (m, 1 H), 3.30–3.26 (m, 1 H), 2.87–2.81 (m, 1 H), 2.68–2.62 (m, 1 H), 2.09–2.02 (m, 2 H), 1.69–1.62 (m, 1 H), 1.53–1.47 (s, 1 H), 1.45–1.39 (m, 2 H), 1.20 (s, 3 H), 1.15 (s, 3 H).

(±)-(1S*,2S*)-*N*-Phenyl-2-indan-1-ylpyrrolidine (V-16). ¹H NMR (400 MHz, *d*₆-C₆H₆) δ 7.33–7.28 (m, 2 H), 7.11–7.04 (m, 3 H), 6.99–6.95 (m, 1 H), 6.82 (td, *J* = 0.8, 7.6 Hz, 1 H), 6.72 (d, *J* = 8.0 Hz, 1 H), 3.86–3.80 (m, 2 H), 3.24–3.19 (m, 1 H), 2.94–2.88 (m, 1 H), 2.86–2.78 (m, 1 H), 2.68–2.60 (m, 1 H), 2.04–1.94 (m, 1 H), 1.61–1.49 (m, 2 H), 1.43–1.36 (m, 1 H), 1.32–1.24 (m, 1 H), 1.14–1.04 (m, 1 H).

Isolation of Oxidative Addition Complex V-9. A flame-dried Schlenk flask under N₂ was charged with Pd(PCy₃)₂ (100 mg, 0.149 mmol), *Z*-7-(2-Bromophenyl)hept-4-en-1-ol (V-6), and 14 mL *d*₆-benzene in the glove box. The reaction mixture was stirred

overnight in a fume hood (outside of glove box). An aliquot was removed to ensure completion of oxidative addition and this was followed by removal of the benzene under reduced pressure. The complex was then dissolved in 3 mL diethyl ether in which it completely dissolved. Therefore the ether was removed under reduced pressure and a 3:1 mixture of pentanes: diethyl ether (4 mL total) was added to the complex. Most of the complex dissolved and the schlenk flask was placed in the glove box freezer. An off-white solid was precipitated and recovered via filtration. The solid was washed with cold pentanes to produce 68 mg of the title compound as a white-grey solid (49%). Data for this molecule is listed below.

Reaction of *Z*-7-(2-Bromophenyl)hept-4-en-1-ol (V-6) with Pd(PCy₃)₂. A flame-dried vial equipped with a stirbar was charged with alcohol **V-6** (3.4 mg, 0.0127 mmol), Pd(PCy₃)₂ (10.0 mg, 0.015 mmol) and 1 mL dry *d*₆-benzene in the glove box. The mixture was stirred in the glove box and then subsequently transferred to an oven-dried NMR tube. The NMR tube was left overnight at room temperature (~10h) until oxidative addition was complete as determined by ¹H and ³¹P NMR spectroscopy. ¹H, ¹H COSY taken of oxidative addition complex. ¹H NMR (400 MHz, *d*₆-C₆H₆) δ 7.62 (d, *J* = 7.6 Hz, 1 H), 7.07–6.95 (m, 3 H), 5.91–5.85 (m, 1 H), 5.60–5.54 (m, 1 H), 3.66 (t, *J* = 8.0 Hz, 2 H), 3.40 (q, *J* = 6 Hz, 2 H), 2.68 (q, *J* = 6.4 Hz, 2 H), 2.22–2.19, 2.05–2.02, 1.90–1.53, 1.52–1.48, 1.35–1.04 (all m, 70 H, PCy₃ and two methylene units). ³¹P {¹H} NMR (161.9 MHz, C₆D₆): δ 20.58 (s, oxidative addition complex **V-9**). Other signals observed in ³¹P spectrum (very minor): δ 45.6 (s, O₂-bound Pd(PCy₃)₂ complex from eq 67), 39.6 (s, Pd(PCy₃)₂).

Reaction of *Z*-8-(2-Bromophenyl)-2-methyloct-5-en-2-ol (V-7) with Pd(PCy₃)₂ (No External Base; Phosphine Behaves as Base). A flame-dried vial equipped with a stirbar was charged with alcohol V-7 (3 mg, 0.0101 mmol), Pd(PCy₃)₂ (7 mg, 0.0104 mmol) and 1 mL dry *d*₆-benzene in the glove box. The mixture was stirred in the glove box and then subsequently transferred to an oven-dried NMR tube. The NMR tube was left overnight at room temperature (~12h) until oxidative addition was complete as determined by ¹H and ³¹P spectroscopy. ¹H NMR (400 MHz, *d*₆-C₆H₆) δ 7.63 (d, *J* = 6.8 Hz, 1 H), 7.08–6.98 (m, 3 H), 5.93–5.86 (m, 1 H), 5.69–5.62 (m, 1 H), 3.69 (t, *J* = 8.4 Hz, 2 H), 2.74–2.68 (m, 2 H), 2.36–2.30 (m, 2 H), 2.22–2.19, 2.05–2.02, 1.90–1.53, 1.52–1.48, 1.35–1.04 (all m, 74 H, PCy₃, one methylene unit, and two methyl units). ³¹P{¹H} NMR (161.9 MHz, C₆D₆): δ 20.54 (s, oxidative addition complex V-10). Other signals observed in ³¹P spectrum: δ 39.6 (left over Pd(PCy₃)₂ complex, δ 45.6 (s, O₂-bound Pd(PCy₃)₂ complex), 45.5 (s, unidentified minor).

The NMR tube was heated to 40 °C and other signals began to form in the ³¹P spectrum, and the oxidative addition peak at δ 20.54 began to get smaller: ³¹P{¹H} NMR (161.9 MHz, C₆D₆): δ 25.47 (s, complex Pd(PCy₃)₂Br₂), 42.77 (s, complex Pd(PCy₃)₂HBr). Other products observed: δ 39.6 (left over Pd(PCy₃)₂ complex, 45.6 (O₂-bound Pd(PCy₃)₂ complex, 46.5 (s, unidentified minor), 20.93 (s, unidentified). After continued heating at 50 °C, the product resulting from syn-addition across the *Z*-olefin (V-15) was observed.

Reaction of *Z*-8-(2-Bromophenyl)-2-methyloct-5-en-2-ol (V-7) with Pd(PCy₃)₂ (With Added External Base-KHMDS). A flame-dried vial equipped with a stirbar was

charged with alcohol **V-7** (3 mg, 0.0101 mmol), Pd(PCy₃)₂ (6.7 mg, 0.0101 mmol) and 1 mL dry *d*₆-benzene in the glove box. The mixture was stirred in the glove box then subsequently transferred to an oven-dried NMR tube. The NMR tube was left overnight at room temperature (~12h) until oxidative addition was complete as determined by ¹H and ³¹P spectroscopy. ¹H NMR (400 MHz, *d*₆-C₆H₆) (same as above complex) δ 7.63 (d, *J* = 6.8 Hz, 1 H), 7.08–6.98 (m, 3 H), 5.93–5.86 (m, 1 H), 5.69–5.62 (m, 1 H), 3.69 (t, *J* = 8.4 Hz, 2 H), 2.74–2.68 (m, 2 H), 2.36–2.30 (m, 2 H), 2.22–2.19, 2.05–2.02, 1.90–1.53, 1.52–1.48, 1.35–1.04 (all m, 74 H, PCy₃, one methylene unit, and two methyl units). ³¹P{¹H} NMR (161.9 MHz, C₆D₆): δ 20.53 (s, oxidative addition complex **V-10**). Other peaks observed: δ 45.6 (s, O₂-bound Pd(PCy₃)₂ complex).

The following day, potassium hexamethyldisilazide was added (2 mg, 0.0101 mmol) to the NMR tube and ¹H NMR analysis revealed the alcohol was deprotonated. The NMR tube was heated to 40 °C for 10 min and the product resulting from anti-addition (**V-14**) across the *Z*-olefin was beginning to form by ¹H NMR spectroscopy as well as the regenerated complex Pd(PCy₃)₂. Data for the deprotonated complex: ¹H NMR (300 MHz, *d*₆-C₆H₆) δ 7.65 (d, *J* = 7.5 Hz, 1 H), 7.22–7.19 (m, 1 H), 7.09–6.98 (m, 2 H), 6.01–5.93 (m, 1 H), 5.91–5.82 (m, 1 H), 3.82–3.67 (m, 2 H), 2.93–2.80 (m, 2 H), 2.39–2.10, 1.91–1.48, 1.35–1.06 (all m, 74 H, PCy₃, one methylene unit, and two methyl units). ³¹P{¹H} NMR (161.9 MHz, C₆D₆): δ 20.53 (s, oxidative addition complex **V-10**), δ 39.7 (s, complex Pd(PCy₃)₂ regenerated), 20.89 (s, unidentified).

The NMR tube was left overnight at 45 °C and the following day, complete conversion to the anti-addition product **V-14** was observed, along with concomitant regeneration of Pd(PCy₃)₂.

Reaction of *Z*-[7-(2-Bromophenyl)hept-4-enyl]aniline (V-8) with Pd(PCy₃)₂. A flame-dried vial equipped with a stirbar was charged with Pd(PCy₃)₂ (7.0 mg, 0.0104 mmol) and 0.75 mL dry *d*₆-benzene in the glove box. The solution was stirred in the glove box and then subsequently transferred to an oven-dried NMR tube. ³¹P NMR analysis revealed two peaks, one corresponding to the complex and the other, the O₂-bound complex. Amine **V-8** was added in aliquots until all the complex was used up and the oxidative addition was complete (1.90 mg total, 0.005 mmol)¹² which took exactly 3 h at RT. At this point NaOtBu (3 mg, 0.031 mmol) was added as a solution in *d*₆-benzene (1 mL) and pyrrolidine **V-16** resulting from syn-addition across the *Z*-olefin began to form at room temperature. VT ¹H NMR was performed heating to 30 °C → 40 °C → 50 °C → 60 °C which resulting in complete conversion to the product pyrrolidine. ¹H NMR of **V-11** (400 MHz, *d*₆-C₆H₆) δ 7.62 (d, *J* = 7.2 Hz, 1 H), 7.20–7.15 (m, 3 H), 7.11–6.95 (m, 2 H), 6.73 (t, *J* = 7.2 Hz, 1 H), 6.51 (d, *J* = 7.2 Hz, 2 H), 5.91–5.84 (m, 1 H), 5.57–5.51 (m, 1 H), 3.65 (t, *J* = 8.8 Hz, 2 H), 2.96–2.90 (m, 2 H), 2.69–2.63 (m, 2 H), 2.21–2.18, 2.05–2.01, 1.83–1.57, 1.29–1.09 (all m, 70 H, PCy₃ and two methylene units). ³¹P {¹H} NMR (161.9 MHz, C₆D₆): δ 20.62 (s, oxidative addition complex **V-11**). Other peaks observed: δ 45.6 (s, O₂-bound Pd(PCy₃)₂ complex).

Figure 12. ^1H NMR spectrum of V-6

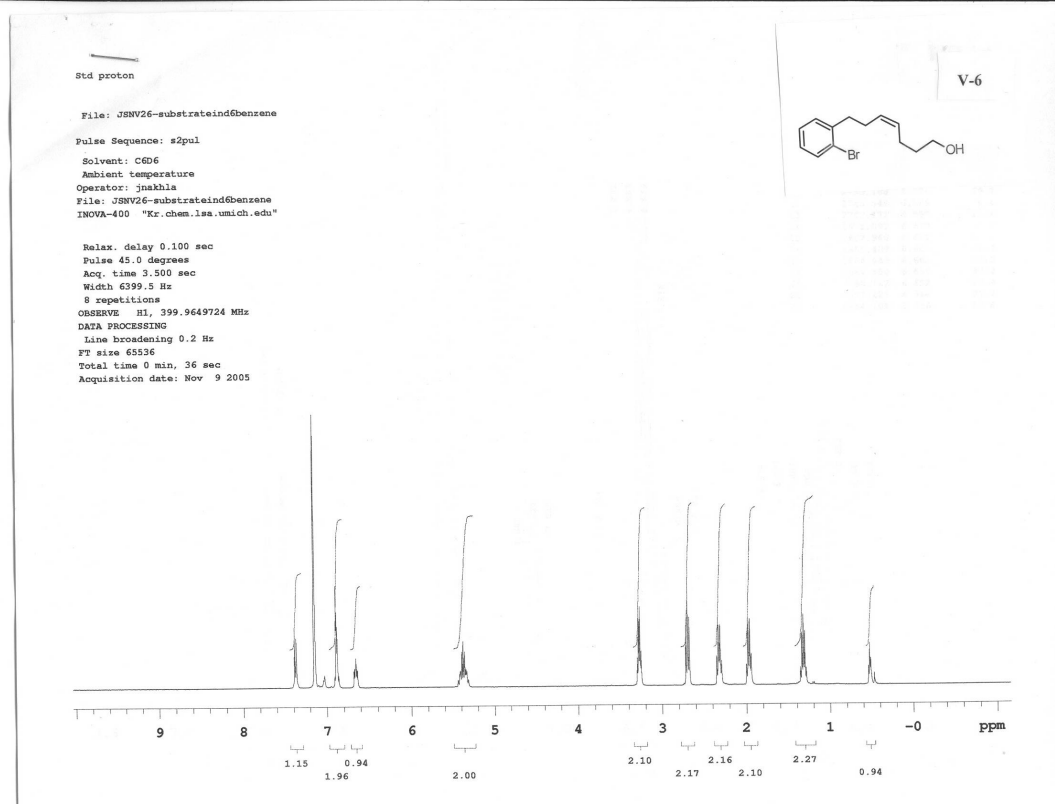


Figure 13. ^1H NMR spectrum of V-7

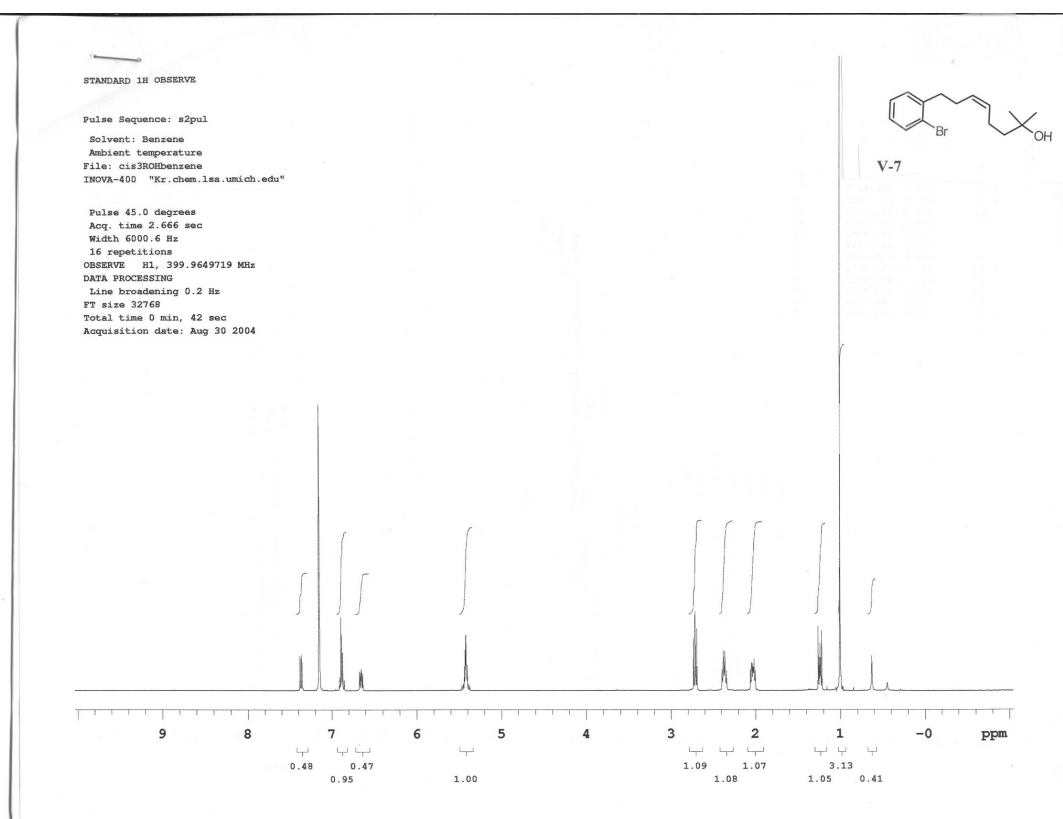


Figure 14. ^1H NMR spectrum of V-8

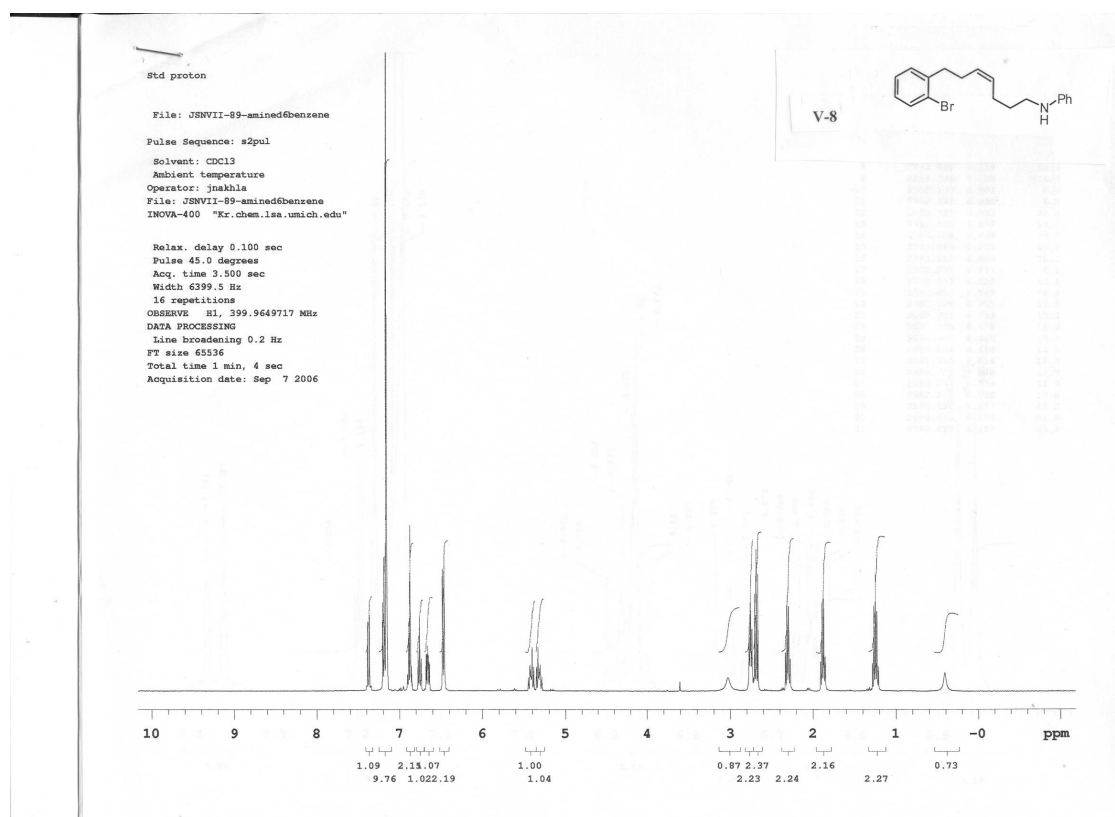


Figure 15. ^1H NMR spectrum of Oxidative Addition Complex V-9

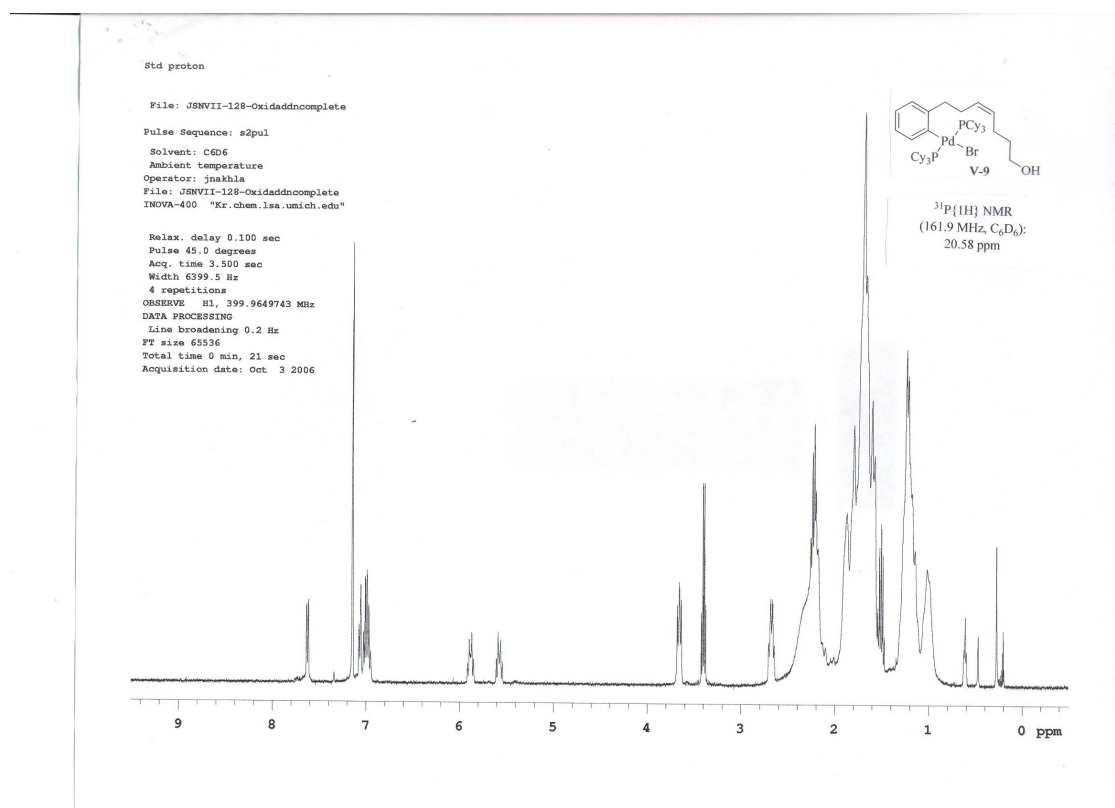


Figure 16. ^1H NMR spectrum of Oxidative Addition Complex V-10

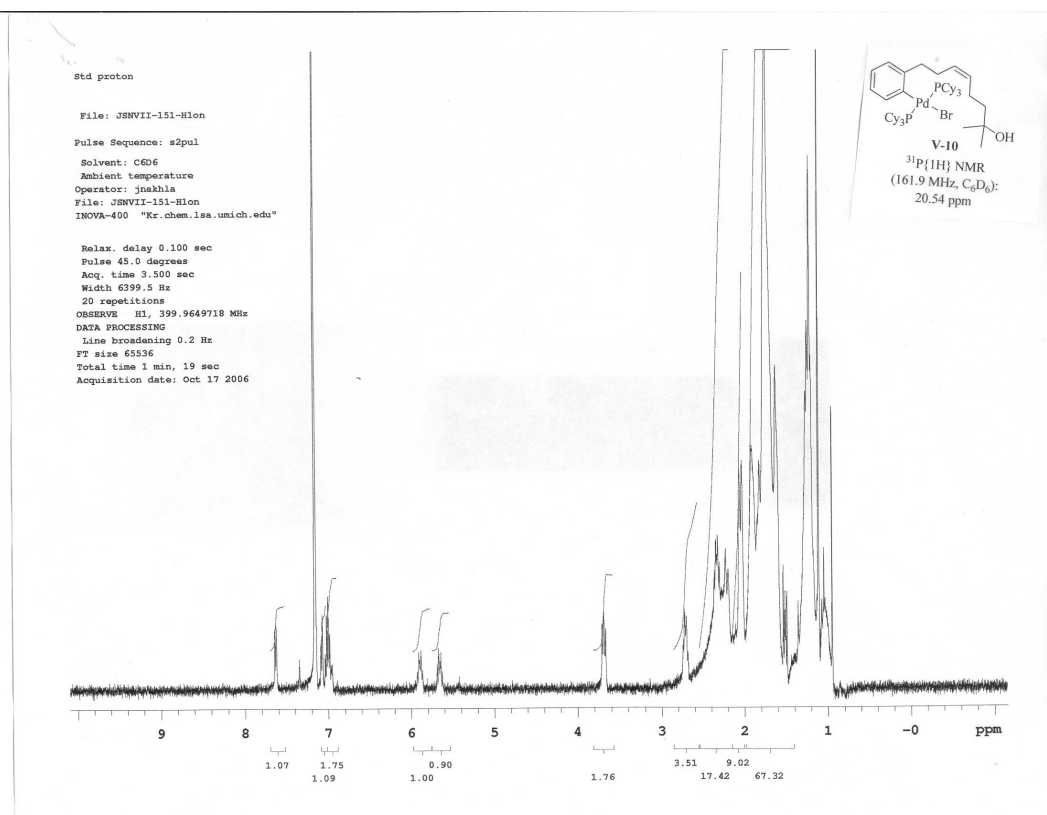


Figure 17. ^1H NMR spectrum of Oxidative Addition Complex V-11

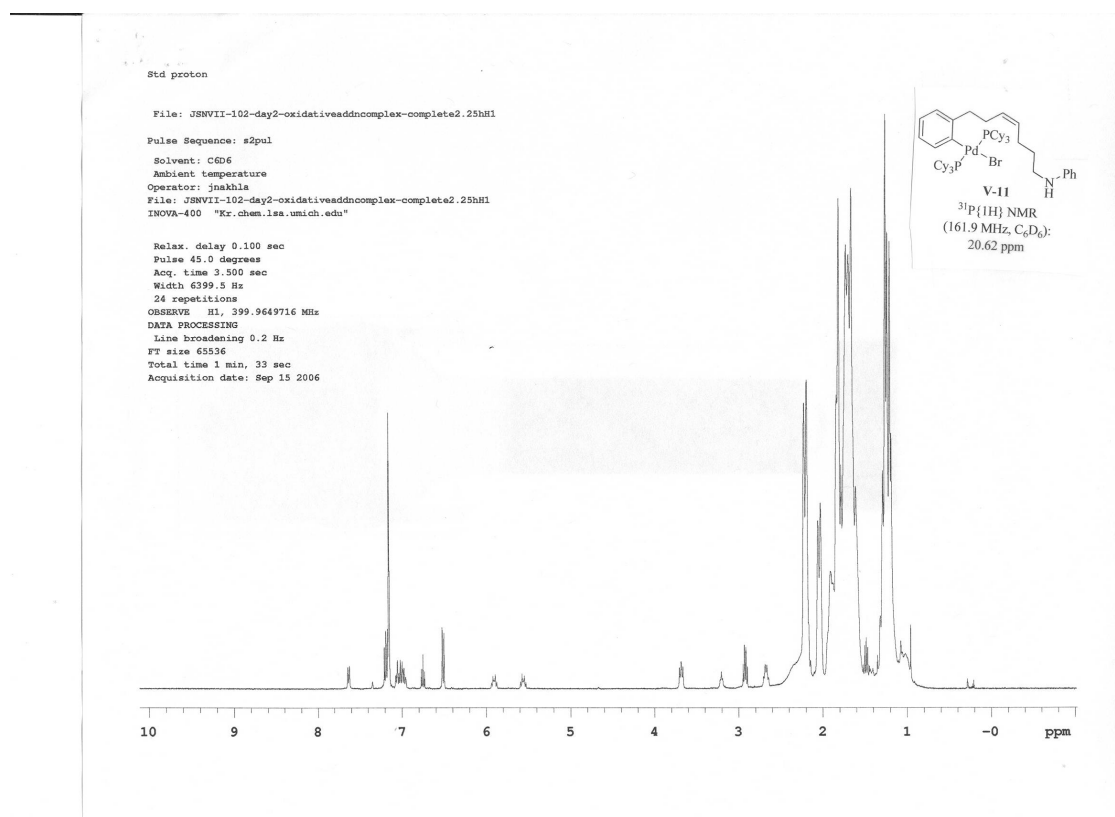


Figure 18. ¹H NMR spectrum of V-13

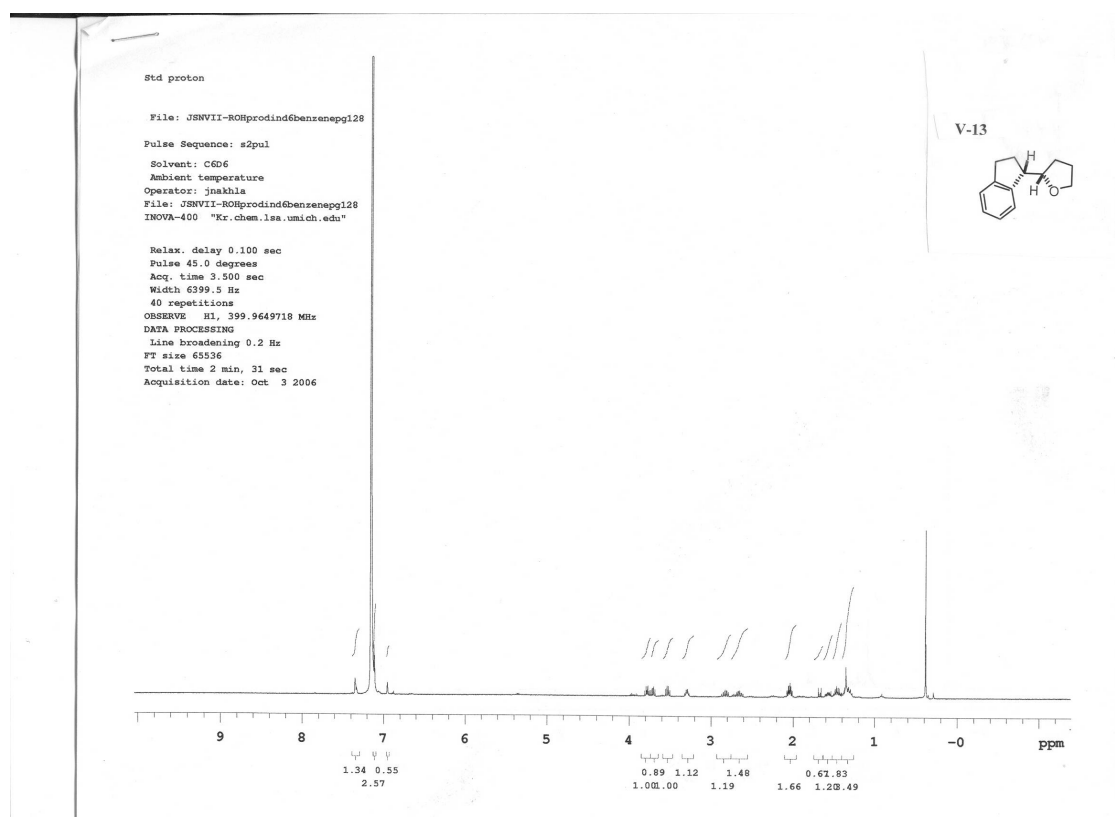


Figure 19. ^1H NMR spectrum of V-13b

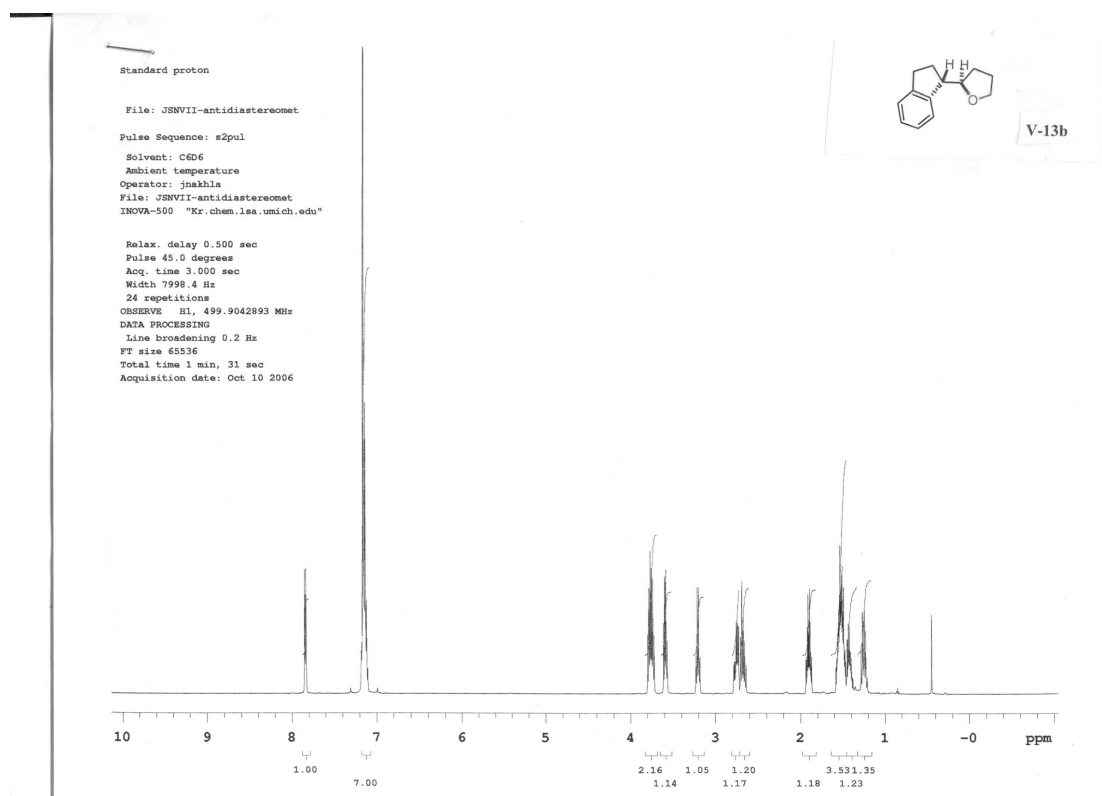


Figure 20. ^1H NMR spectrum of V-14

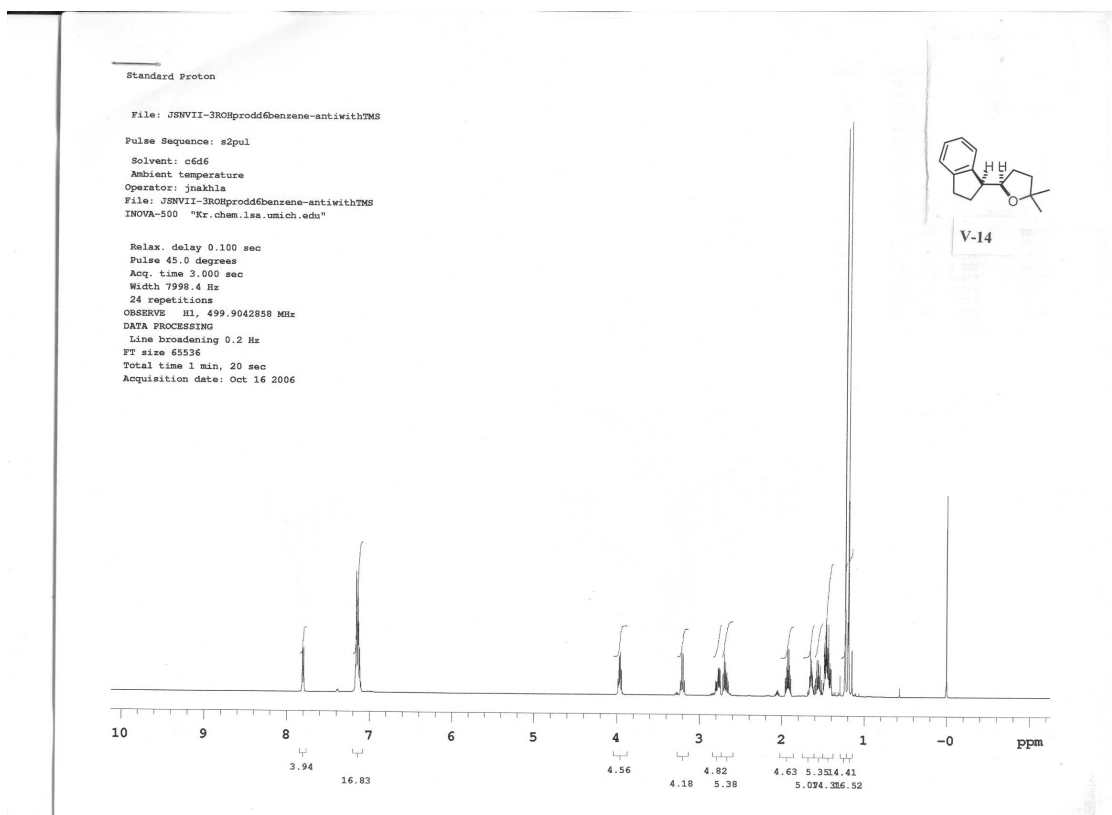


Figure 21. ^1H NMR spectrum of V-15

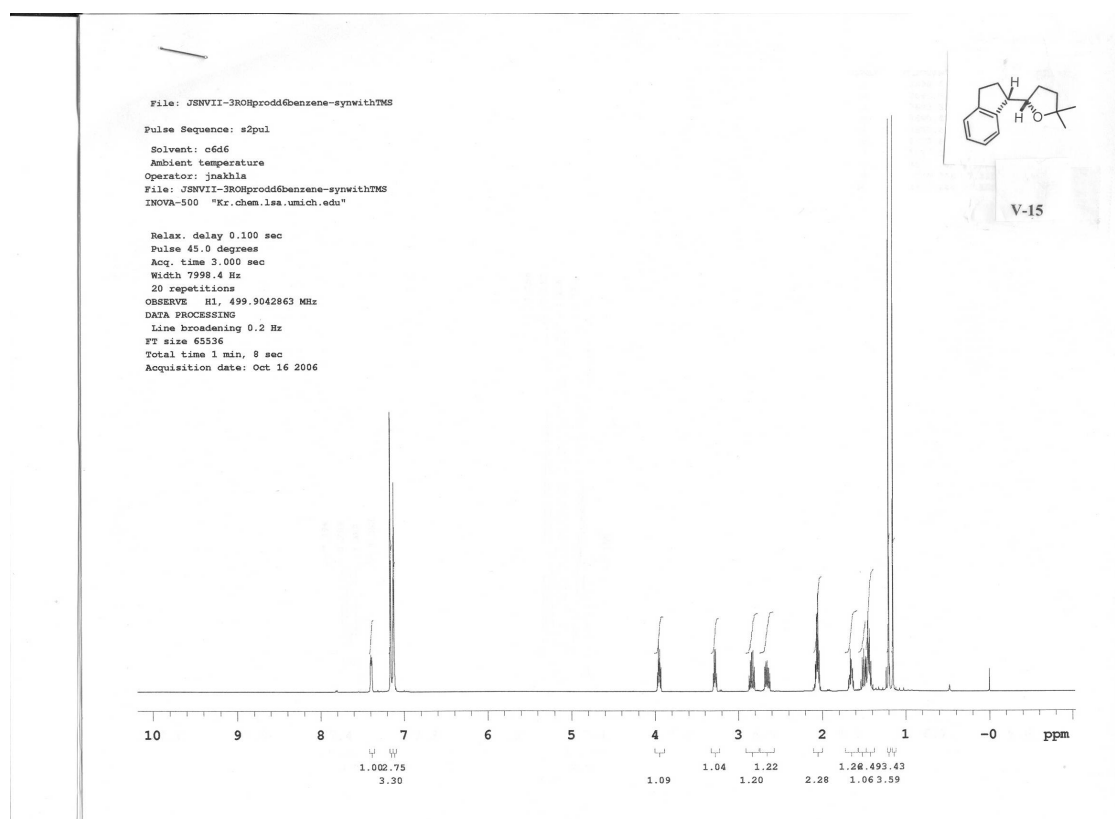


Figure 22. ^1H NMR spectrum of V-16

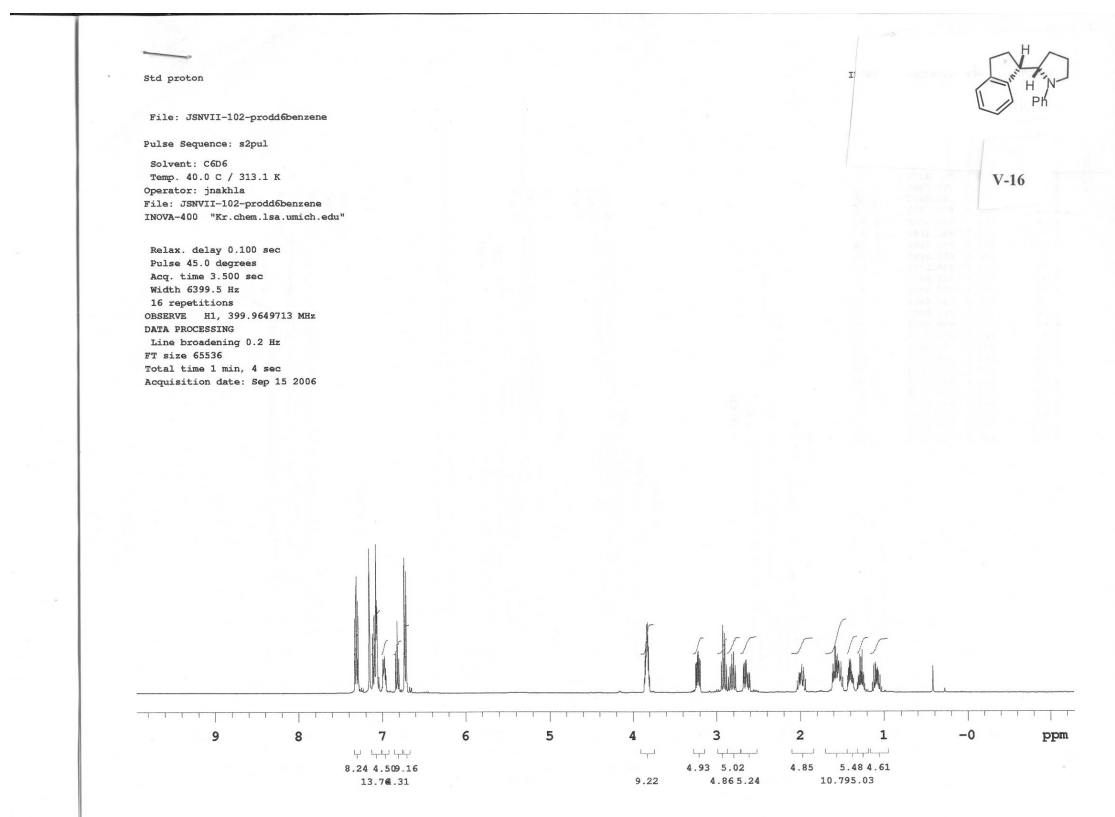


Figure 23. ^1H , ^1H -NMR COSY of Oxidative Addition Complex V-9

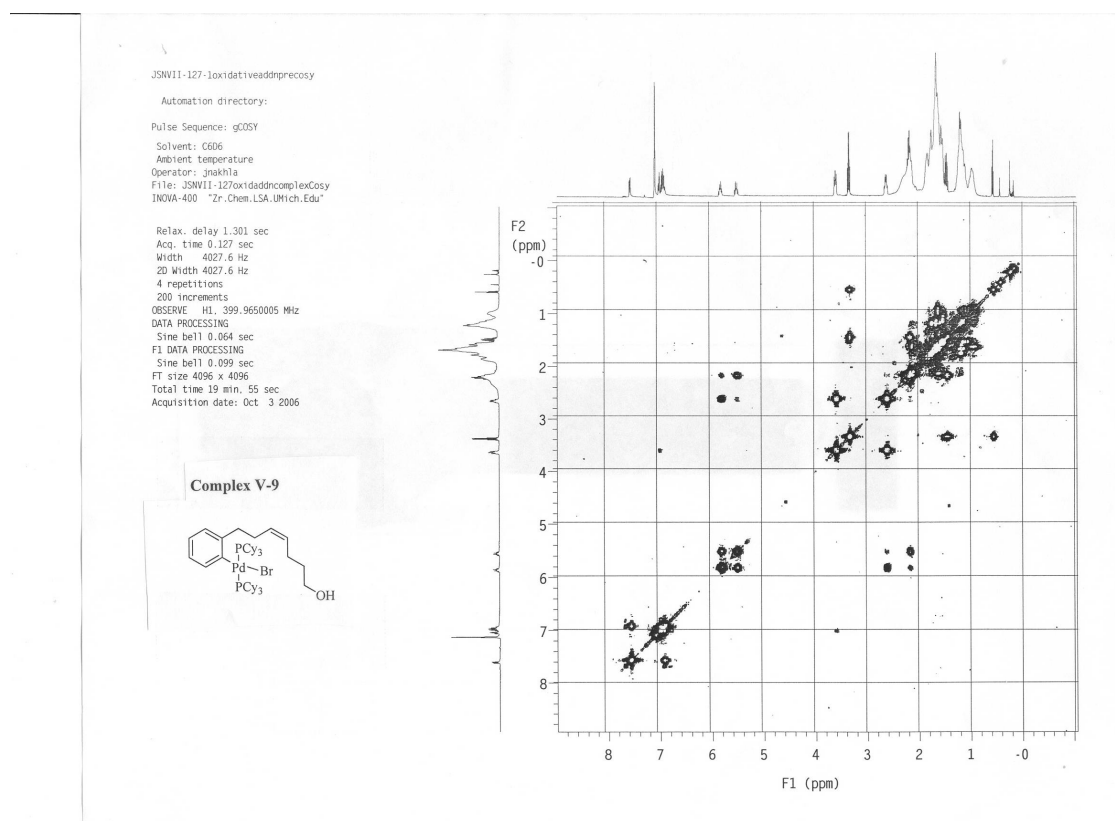
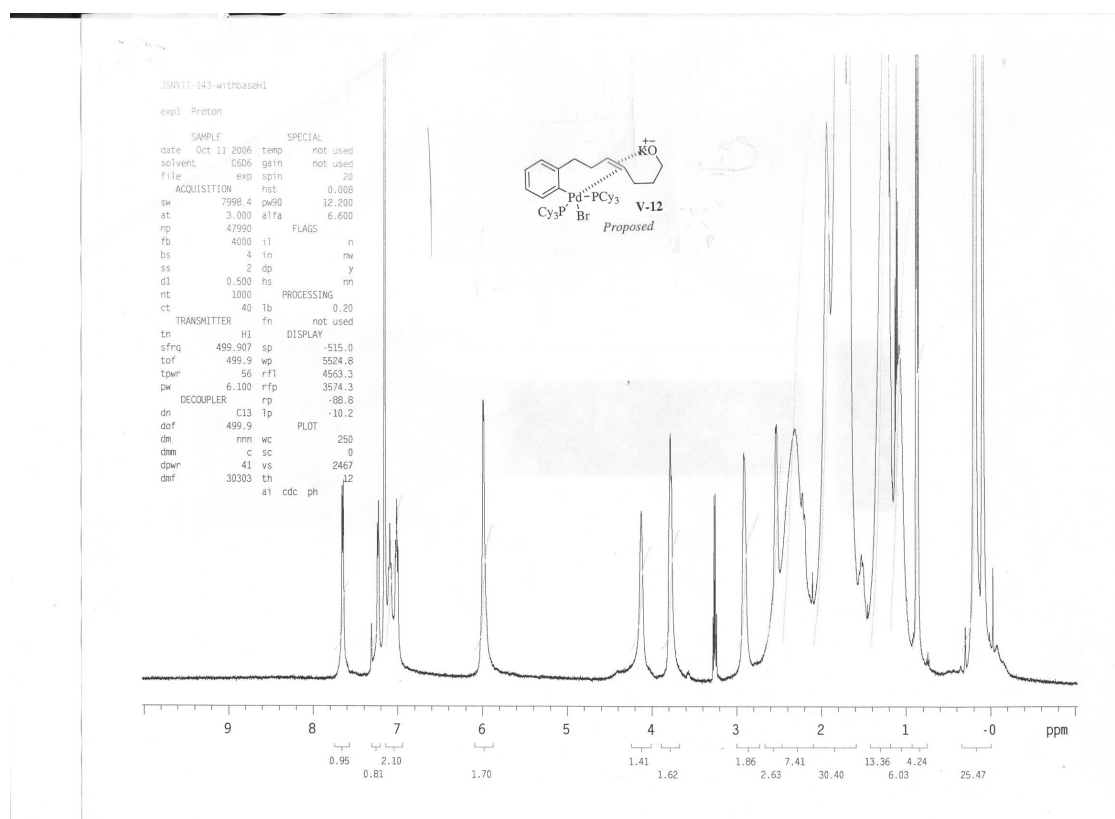


Figure 24. ^1H NMR spectrum of V-12



References

- ¹ Reproduced in part with permission from “Intramolecular Pd-Catalyzed Carboetherification and Carboamination. Influence of Catalyst Structure on Reaction Mechanism and Product Stereochemistry” Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893–2901. Copyright 2006 American Chemical Society.
- ² For examples of Pd-catalyzed *N*-arylation reactions that likely proceed through macrocyclic palladium(aryl)(amido) complexes, see: Beletskaya, I. P.; Bessmertnykh, A. G.; Averin, A. D.; Denat, F.; Guillard, R. *Eur. J. Org. Chem.* **2005**, 281–305 and references therein.
- ³ (a) Galardon, E.; Ramdeehul, S.; Brown, J. M.; Cowley, A.; Hii, K. K.; Jutand, A. *Angew. Chem. Int. Ed.* **2002**, *114*, 1838–1841. (b) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030–3039. (c) Tatsuno, Y.; Yoshida, T.; Otsuka, S. *Inorg. Syntheses* **1990**, *28*, 342.
- ⁴ Yoshida, T.; Otsuka, S. *J. Am. Chem. Soc.* **1977**, *99*, 2134–2140.
- ⁵ Stambuli, J. P.; Incarvito, C. D.; Buhl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 1184–1194.
- ⁶ (a) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755–2763. (b) Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504–6511.
- ⁷ Cross, W. I.; Godfrey, S. M.; Jackson, S. L.; McAuliffe, C. A.; Pritchard, R. G. *J. Chem. Soc., Dalton Trans.* **1999**, 2225–2230.
- ⁸ At the time we conducted the experiments with amine **V-8**, we did not know the source of impurity in Pd(PCy₃)₂, or how to remove it.
- ⁹ Galardon, E.; Ramdeehul, S.; Brown, J. M.; Cowley, A.; Hii, K. K.; Jutand, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1760–1763.
- ¹⁰ (a) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2745–2754. (b) Vicente, J.; Abad, J.-A.; Martinez-Vicente, E.; Ramirez de Arellano, M. C. *Organometallics* **2000**, *19*, 752–760. (c) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969–5970.
- ¹¹ (a) Clarke, M. L.; Orpen, A. G.; Pringle, P. G.; Turley, E. *Dalton Trans.* **2003**, 4393–4394. (b) Munakata, H.; Green, M. L. H. *Chem. Comm.* **1970**, 881–882. (c) Green, M. L. H.; Munakata, H.; Saito, T. *J. Chem. Soc. A.* **1971**, 469–474.
- ¹² This experiment was performed early on in the stoichiometric investigation. At the time, we did not know the identity of the O₂-bound Pd(PCy₃)₂ complex and therefore did not know how to remove it from the mixture.