DESIGNS, SYNTHESES, AND APPLICATIONS OF N-HETEROCYCLIC AND ACYCLIC DIAMINOCARBENE-METAL COMPLEXES

By

SEBASTIEN INAGAKI

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2012

“To my parents who believed in me and in my dreams”

ACKNOWLEDGMENTS

I wish to thank my advisor Sukwon Hong for his help throughout my whole Ph. D. program. The fruitful discussions and his wise words were very helpful. He knew how to be patient and supportive with my work.

I also want to thank my co-workers: Dr. Dimitri Hirsh-Weil, Dr. David Snead, and Dr. Hwimin Seo who I worked closely with. Their work ethic was no doubt helpful to me and I will always appreciate their research skills. I finally thank my other co-workers: Dr. Mike Rodig, Dr. Kai Lang, and Dr. Jongwoo Park for some interesting discussions I had with them.

TABLE OF CONTENTS

page

ACKNOWLEDGMENTS 4

LIST OF TABLES 7

LIST OF FIGURES 8

LIST OF SCHEMES 12

ABSTRACT 14

CHAPTER

1 INTRODUCTION 15

Electronic Properties of NHC Ligands 15
Applications of NHC-Metal Complexes as Catalysts 16
Recent Advances in the Synthesis of Chiral NHC Ligands 18
Chirality on the Backbone 18
Chirality on the Substituent of the Nitrogen Atom 23
Chirality at the α-position from the nitrogen atom 23
Chirality at the γ-position from the nitrogen atom 27
Ligands containing chiral planes 31
Synthesis of Acyclic Diaminocarbene Ligands 35
Formation of a Carbene Intermediate 35
ADC-Metal Complexes by Functionalization of Isocyanide 36
First Isolation of a Free ADC 37
ADC-Metal Complexes by Complexation of Free Carbene 38
ADC-Metal Complexes by Oxidative Addition 40
Applications of ADC-Palladium Complexes in Coupling Reactions 42
Aryl Substituted ADC-Metal Complexes 42
Return to the Original Preparation 45
Chiral Acyclic Diaminocarbene Ligands 47

2 DESIGN, SYNTHESIS, AND APPLICATIONS OF CHIRAL N-HETEROCYCLIC CARBENE-METAL COMPLEXES 49

Previous Designs of Chiral NHC Ligands 49
Improvement of the Original Design 53
Synthesis of the New C_1-Symmetric Carbene Ligand 55
Applications of the New C_1-Symmetric NHC Ligand 56
Design of a Ligand Containing a Lewis Base 63
Experimental Section 69
General Remarks 69
Synthesis of Imidazolium *ent*-2-15dc 69

Synthesis of Imidazolium *ent*-2-15ec 75
β-Borylation Reaction of Conjugated Ester 2-30 or Conjugated Amide 2-13a .. 81
Typical procedure 81
HPLC spectra for amide 2-14a 82
HPLC spectra for ester 2-31 83
1,2-Addition Reaction 83
Typical procedure 83
Characterization of 1,2-addition products (Table 2-3) 84
HPLC spectra for the ligand scope (Table 2-4) 84
Asymmetric Allylic Alkylation 86
Typical procedure 86
NMR spectra for the regioselectivity 86
HPLC spectra for the ligand scope 87

3 DESIGN, SYNTHESIS, AND APPLICATIONS OF CHIRAL AND ACHIRAL ACYCLIC DIAMINOCARBENE-METAL COMPLEXES 89

Achiral Acyclic Diaminocarbene Metal Complexes 89
ADC-Copper Catalyzed Allylic Alkylation 89
ADC-Iridium Complex 93
Design and synthesis of an ADC-iridium complex 93
Hydroboration of alkenes 97
Chiral Acyclic Diaminocarbene Precursors 101
Original Design of a Chiral Acyclic Diaminocarbene 101
New Design of a Chiral Acyclic Diaminocarbene 102
Experimental Section 105
ADC-Copper Catalyzed Allylic Alkylation 105
Typical procedure for allylic alkylation 105
Characterizations of products 3-4a-f 106
ADC-Iridium Complexes 107
Syntheses of iridium complexes 107
Typical procedure for the hydroboration 111
NMR spectra 112
Chiral Acyclic Diaminocarbene Metal Complexes 113
Synthesis of chloroamidinium salt 3-40 113
Syntheses of ADC-metal complexes 3-41 and 3-42 114
Suzuki cross-coupling reaction 116
1,2-Addition of 1-naphthylboronic acid to *o*-anisaldehyde 117

4 CONCLUSION 119

LIST OF REFERENCES 121

LIST OF TABLES

Table		page
1-1	Ligand scope for the desymmetrization of diynesulfonamide **1-36**	26
1-2	Carbene precursor scope for the conjugate addition of EtMgBr on enone **1-50**	29
2-1	Optimization of the reaction conditions	59
2-2	Base scope for the generation of the free carbene	60
2-3	Substrate scope	61
2-4	Chiral ligand scope	62
3-1	Optimization of conditions for the copper catalyzed allylic alkylation	90
3-2	Substrate scope for ADC-copper catalyzed allylic alkylation	91

LIST OF FIGURES

Figure		page
1-1	Structures of imidazolin-2-ylidene and imidazol-2-ylidene	15
1-2	The two ground states adopted by the NHC carbene and stabilization of the singlet state	15
1-3	Structures of Grubbs catalysts	16
1-4	NHC-Ir catalyzed hydrogen transfer	16
1-5	Uses of NHC-Pd catalysts in coupling reactions	17
1-6	NHC-gold catalyzed of cycloisomerization of 1,5-enyne	17
1-7	Ruthenium-catalyzed desymmetrization of triene **1-4**	19
1-8	Ruthenium-catalyzed AROCM of norbornene **1-14**	21
1-9	Palladium-catalyzed asymmetric diamination of conjugated dienes **1-17**	22
1-10	Palladium-catalyzed intramolecular α-arylation of amide **1-21**	22
1-11	Herrmann's preparation of chiral imidazoliums	23
1-12	Rhodium-catalyzed hydrosilylation of acetophenone **1-25**	23
1-13	Czekelius chiral imidazolinium **1-27**	24
1-14	Substituent scope of NHC-gold complex **1-35**	25
1-15	Herrmann's rhodium catalysts	27
1-16	Rhodium-catalyzed hydrosilylation of acetophenone **1-25**	27
1-17	Rhodium-catalyzed hydrosilylation of pyruvic acid esters **1-44**	27
1-18	Copper-catalyzed hydrosilylation of acetophenone **1-25**	28
1-19	Palladium-catalyzed oxidative Heck reaction of enone **1-52**	30
1-20	Copper-catalyzed conjugate addition of dialkylzinc to cyclic enones	31
1-21	Ruthenium-catalyzed AROM of norbonene **1-14**	32
1-22	Gold-catalyzed intramolecular hydroamination of **1-59**	32

1-23 Rhodium-catalyzed 1,2-addition of arylboronic acids onto benzaldehyde derivatives 35

1-24 Dimerization of imidazolinium **1-76** and formamidinium **1-78** 35

1-25 First ADC-metal carbene synthesized 36

1-26 N-C-N bond angles of free carbenes and carbene-copper complexes 37

1-27 Deprotonation of formamidinium **1-83** 38

1-28 π-back-donation of the metal to a C=O ligand 40

1-29 Comparison of CO frequencies between ADC- and NHC-Rh complexes 40

1-30 Palladium-catalyzed Heck reaction 41

1-31 Common free NHC ligands 42

1-32 Possible conformers of Bielawski's ADC-metal complexes 43

1-33 X-ray structure of Rh-complex **1-99** in its *amphi*-conformation 43

1-34 Stereoselectivity of Bielawski's ruthenium complexes in cross metathesis 44

1-35 Espinet's hydrogen bond supported heterocyclic carbene (HBHC)-gold complex **1-100** 45

1-36 Hashmi's preparation of ADC-gold complexes 45

1-37 ADC-gold catalyzed tandem reaction 46

1-38 Hashmi's complexes in the Suzuki-Miyaura coupling 47

1-39 The free rotation around the C-N bond allowed for ADC ligands 47

1-40 Toste's enantioselective gold-catalyzed cyclization of **1-111** 48

1-41 Slaughter's enantioselective gold-catalyzed cyclization of **1-114** 48

2-1 Copper-catalyzed allylic alkylation with Hong's NHC-Cu complex 50

2-2 Copper-catalyzed β-borylation with Hong's C_1-symmetric NHC 51

2-3 Origin of the chiral isoquinoline moiety for C_1- and C_2-symmetric ligands 52

2-4 Retrosynthesis for the preparation of the chiral isoquinoline moiety 53

2-5 First rhodium-catalyzed 1,2-addition 56

2-6 NHC-rhodium catalyzed asymmetric 1,2-addition 57
2-7 Ma's NHC as ligand for asymmetric the 1,2-addition 57
2-8 Shi's bis(carbene)-Pd complexes in the asymmetric 1,2-addition 57
2-9 Copper-catalyzed 1,2-addition 58
2-10 Comparison of ligands ***ent*-2-15dc** and **2-15bc** in the β-borylation of **2-13a** 63
2-11 New concept for the ring opening of the aziridine moiety 63
2-12 Calculated energy levels of protonated 1-methyl-4-phenyl-1,2,3-triazole 66
2-13 Comparison of ligands ***ent*-2-15ec** and **2-15bc** for the β-borylation of **2-30** 67
2-14 Comparison of ligands ***ent*-2-15ec** and **2-15bc** for the 1,2-addition 67
2-16 HPLC spectra for the β-borylation of amide **2-14a** 82
2-17 HPLC spectra for the β-borylation of ester **2-31a** 83
2-18 HPLC spectra of the 1,2-addition product (racemic mixture) 84
2-19 HPLC spectra of the 1,2-addition product (Table 1, entry 1) 85
2-20 HPLC spectra of the 1,2-addition product (Table 1, entry 2) 85
2-20 HPLC spectra of the 1,2-addition product (Table 1, entry 3) 85
2-21 HPLC spectra of the 1,2-addition product (Table 1, entry 4) 86
2-22 NMR spectra of the product of the AAA with ***ent*-2-15ec** 87
2-23 HPLC spectra of product **2-33** (racemic mixture) 87
2-24 HPLC spectra of product **2-33** with ***ent*-2-15ec** 88
2-25 HPLC spectra of product **2-33** with with ***ent*-2-5aa** 88
2-26 HPLC spectra of product **2-33** with ***ent*-2-15ec** at -78°C 88
3-1 Catalytic activity of **3-2** in asymmetric allylic alkylation 89
3-2 Possible conformers of the new acyclic diaminocarbene ligand 94
3-3 Thiourea formation: trapping method of carbene intermediate 95
3-4 X-ray structures of complex **3-23a** 96

3-5 X-ray structure of Bielawski's ADC-iridium complex 97
3-6 Oxidative addition of catecholborane to Wilkinson's reagent 98
3-7 First rhodium-catalyzed hydroboration 98
3-8 Mechanism of rhodium-catalyzed hydroboration of terminal olefins 99
3-9 Iridium-catalyzed hydroboration of styrene 100
3-10 Original design of a chiral ADC ligand 101
3-11 Preparation of the chiral ADC-metal complex 101
3-12 ADC-palladium catalyzed Suzuki-Miyaura coupling reaction 104
3-13 ADC-rhodium catalyzed 1,2-addition reaction 104
3-14 Undesired conformations of the ADC metal complexes 105
3-15 NMR spectra of the hydroboration product 112
3-16 HPLC spectra of the Suzuki-Miyaura coupling product 117
3-17 HPLC spectra of the 1,2-addition product 118
4-1 New chiral NHC precursors 119
4-2 New ADC-iridium complex **3-22a** 120
4-3 Chiral ADC ligand precursors 120

LIST OF SCHEMES

Scheme		page
1-1	Grubbs' synthesis of chiral imidazoliniums	18
1-2	Synthesis of Blechert's chiral NHC-ruthenium complex	20
1-3	Synthesis of Czekelius' chiral NHC-gold complexes **1-32a-h**	24
1-4	Synthesis of Sakaguchi's chiral imidazoliums	31
1-5	Synthesis of Shi's chiral NHC-gold complex **1-61**	33
1-6	Preparation of enantiopure atropisomer **(*S*)-1-62**	33
1-7	Preparation of enantiopure paracyclophane **(S_p)-1-70a**	34
1-8	Synthesis of Ma's chiral imidazolium **1-71a-e** and **1-73a-d**	34
1-9	Formation of free acyclic diaminocarbene	37
1-10	Alder's proposed mechanism for the dimerization of free carbene	38
1-11	Herrmann's preparation of ADC-metal complexes	39
1-12	Fürstner's oxidative addition of a chloroamidinium on palladium(0)	41
1-13	Preparation of neutral and cationic ADC-palladium complexes	41
1-14	Use of ADC-Pd complexes in coupling reactions	42
1-15	Hashmi's preparation of ADC- and NHC-palladium complexes	46
2-1	Preparation of Hong's NHC-metal complexes	49
2-2	Preparation of Hong's C_1-symmetric NHC ligands and their metal complexes	50
2-3	Preparation of the chiral free amine **2-2**	52
2-4	Formation of structural isomers after Bischler-Napieralski cyclization	54
2-5	New target for the chiral isoquinoline moiety	54
2-6	Preparation of amine ***ent*-2-2d**	55
2-7	Formation of imidazolium ***ent*-2-15dc**	55
2-8	New targets for the chiral amine containing a potential Lewis base	64

2-9 Synthesis of free amine ***ent*-2-2e** 65

2-10 Synthesis of imidazolium ***ent*-2-15ec** 66

3-1 Evidence of the formation of the ADC-copper complex 92

3-2 Possible mechanisms for the formation of the ADC-organocopper(I) 93

3-3 Synthesis of ADC-iridium complex 95

3-4 Hydroboration of alkenes by a) Woods and b) Brown 98

3-5 Preparation of the chiral pyrrolidine **3-27** 102

3-6 Synthesis of chloroamidinium **3-40** 103

3-7 Formation of chiral ADC-Pd **3-41** and ADC-Rh **3-42** complexes 103

Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

DESIGNS, SYNTHESES, AND APPLICATIONS OF N-HETEROCYCLIC AND ACYCLIC DIAMINOCARBENE-METAL COMPLEXES

By

Sébastien Inagaki

May 2012

Chair: Sukwon Hong
Major: Chemistry

The design of a chiral isoquinoline-based N-heterocyclic carbene was revisited. Two ligands, one containing a Lewis base, were synthesized. The corresponding carbene-metal complexes were then used in different catalytic and asymmetric systems to seek greater reactivity and enantioselectivity.

Acyclic diaminocarbene ligands have also a potential in asymmetric synthesis. However, their backbones make it more challenging to control their enantioselectivity. Simple achiral ADC-metal complexes could also achieve good reactivity with a new method of generating them in situ. A new ADC-iridium complex was synthesized and its X-ray structure was obtained showing the presence of only one conformer of the ligand.

CHAPTER 1
INTRODUCTION

Electronic Properties of NHC Ligands

Carbenes derived from imidazolin-2-ylidene or imidazol-2-ylidene skeleton (Figure 1-1) can exist either as a singlet or a triplet ground state.[1] However, the singlet state is more favored over the triplet one due to the neighboring nitrogen atoms (Figure 1-2). Indeed, their σ-withdrawing character by inductive effect stabilizes the filled σ orbital of the $C_{carbene}$. Besides, their π-donation by resonance effect towards the empty p_π orbital of the $C_{carbene}$ further stabilizes the singlet state. When the gap between the two states is lower than about 40 kcal.mol^{-1}, then the preference for the singlet state is less important.[2, 3]

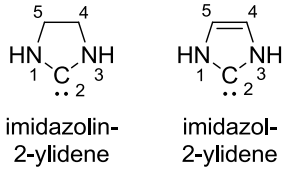


Figure 1-1. Structures of imidazolin-2-ylidene and imidazol-2-ylidene

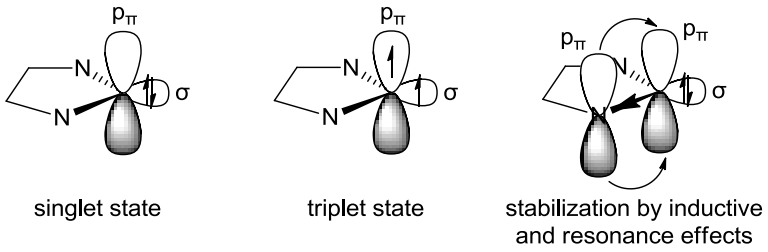


Figure 1-2. The two ground states adopted by the NHC carbene and stabilization of the singlet state

This stabilization from the nitrogen atoms makes the carbenes air and moisture resistant.[4, 5] Besides, it confers on them a more nucleophilic character (more σ-donor) than the phosphines meaning they have stronger bonding to metals. All these features

make carbenes a new class of ligands of interest. Complexes with late transition metals have first been studied such as ruthenium, iridium, palladium, and gold.

Applications of NHC-Metal Complexes as Catalysts

One of the most famous examples of a NHC-ruthenium complex was the olefin metathesis performed by Grubbs in 1999.[6] He modified his first generation catalyst by substituting one of the phosphine ligands by SIMes carbene (Figure 1-3). The new complex gave higher activity than its phosphine analogue with a more extended substrate scope and in a lower catalyst loading. This difference in activity could be explained by the binding affinity between the phosphines versus the olefin. Indeed, the first generation catalyst had a better preference for binding to phosphines over olefins by four orders of magnitude than the second generation.

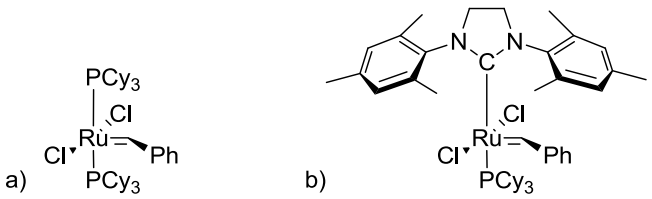


Figure 1-3. Structures of Grubbs catalysts a) first generation and b) second generation

Hydrogen transfer was one of the first test reactions for NHC-iridium complexes. In 2001, Nolan used cationic $[Ir(cod)(py)(ICy)]PF_6$ in very low catalyst loading (0.025 mol%) for the hydrogen transfer to ketones and alkenes in isopropanol with very good reactivities (Figure 1-4).[7]

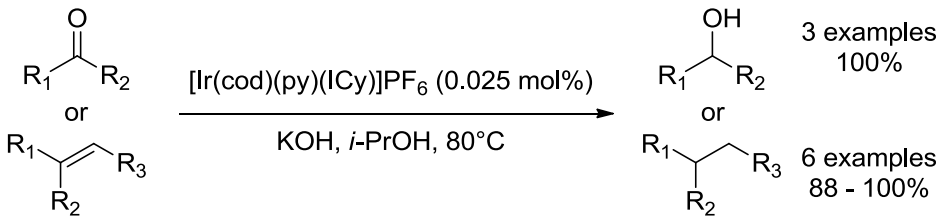


Figure 1-4. NHC-Ir catalyzed hydrogen transfer

Also Nolan reported the use of imidazoliums as carbene precursors for palladium-catalyzed coupling reactions such as Suzuki-Miyaura,[8] Stille,[9] Kumada,[10] Hiyama,[11] or amination[12] reactions. He was able to use most of the time the less reactive coupling partners, aryl chlorides, to obtain the desired products in good yields (Figure 1-5).

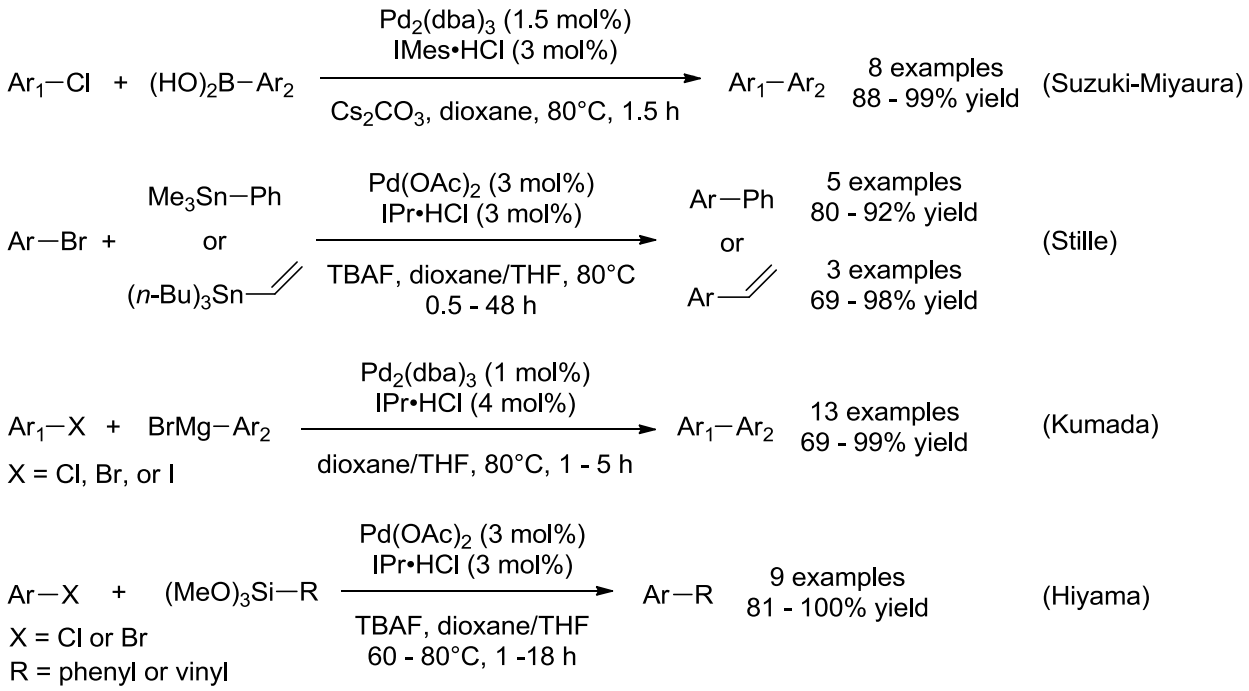


Figure 1-5. Uses of NHC-Pd catalysts in coupling reactions

Finally, in collaboration with Malacria, Nolan studied the gold-catalyzed of enyne cyclizations.[13] They were able to optimize the conditions to favor the formation of only one constitutional isomer in good yield (Figure 1-6).

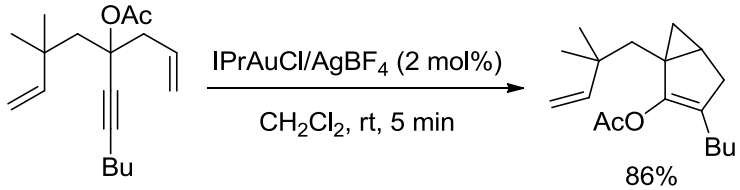


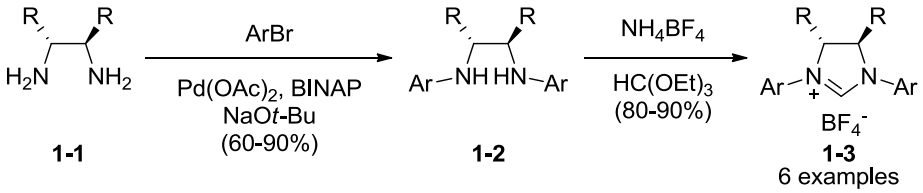
Figure 1-6. NHC-gold catalyzed of cycloisomerization of 1,5-enyne

Recent Advances in the Synthesis of Chiral NHC Ligands

NHC ligands can have their chiral sites either on their backbones or on the substituents of the nitrogen atoms. While the first choice is easy access from an optically active diamine, the source of chirality is far away from the metal. However, the second method requires more steps to obtain the desired material but the chiral site is closer to the metal sphere.

Chirality on the Backbone

One of the pioneers to design NHC ligands with the chirality on the backbone was Grubbs when he first reported the synthesis of imidazoliniums **1-3** in 2001.[14] He used commercially available chiral 1,2-disubstituted ethylenediamines that he arylated and then cyclized. In only two steps he was able to obtain a variety of optically pure imidazoliniums as carbene precursors (Scheme 1-1).



Scheme 1-1. Grubbs' synthesis of chiral imidazoliniums

The drawback of this design was to have the source of the chirality remote from the metal center. Therefore, the use of an *ortho*-monosubstituted aryl group (e.g.: *o*-methylphenyl or *o*-isopropylphenyl) on the nitrogen atoms was required to relay the stereoinformation from the back of the ligand to the front.

The authors used this design for the desymmetrization of achiral trienes **1-4** via the ruthenium-catalyzed ring-closing metathesis obtaining up to 90% ee (Figure 1-7).

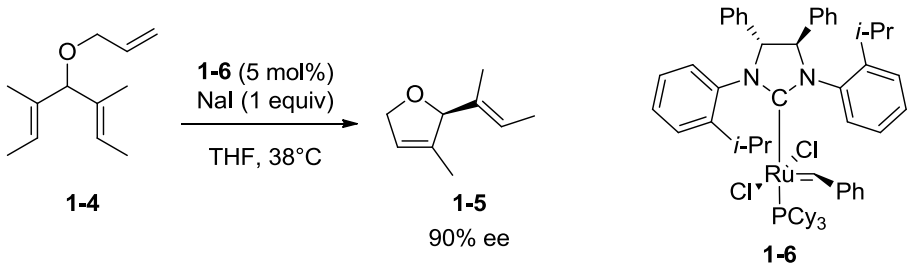
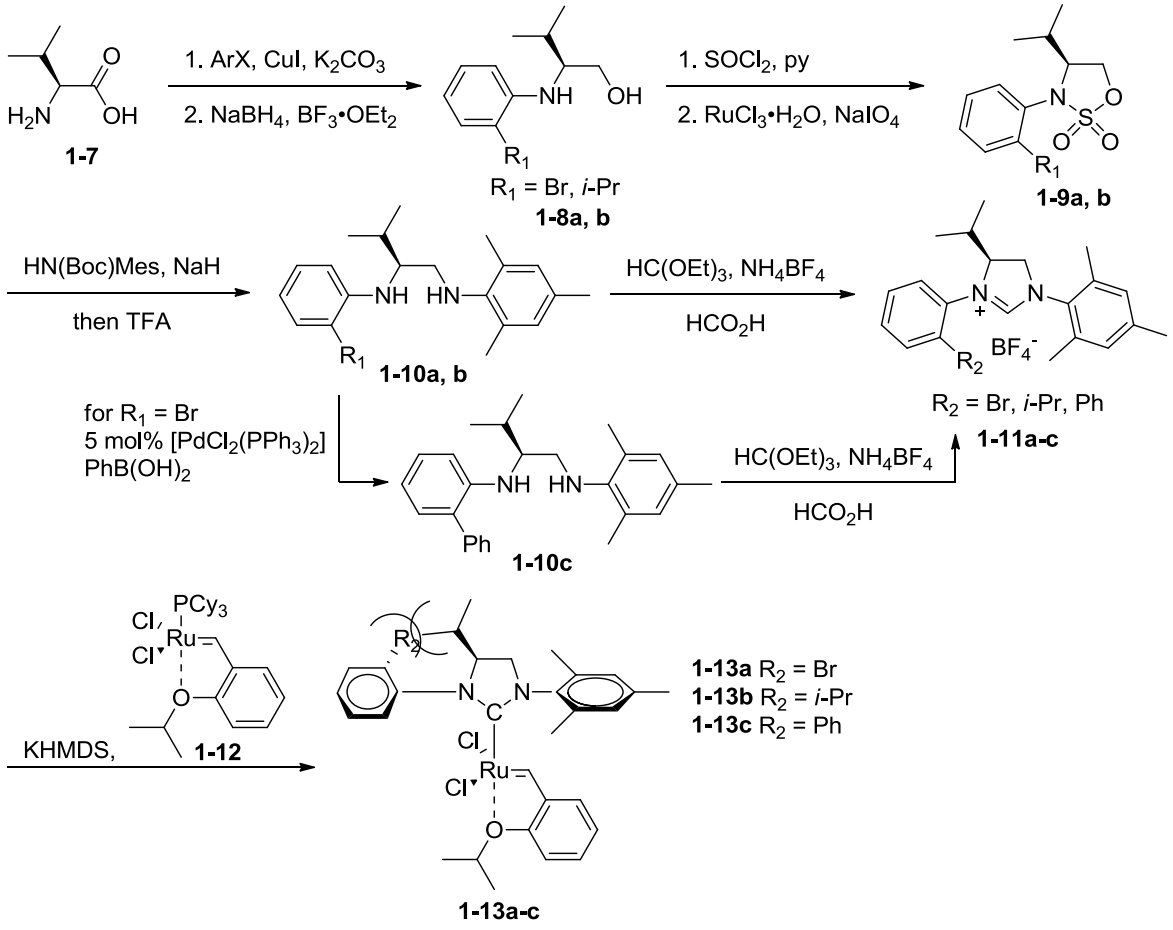


Figure 1-7. Ruthenium-catalyzed desymmetrization of triene **1-4**

The substituents at the 4' and 5' positions on Grubbs catalyst, not only had a role in the stereoinduction, but they also made the catalyst more stable. Indeed, Grubbs studied the substitution effect of the backbone with methyl groups.[15] He found out that the more substituted the backbone was, the closer the carbene was to the metal center due to the ligand being electron rich. Therefore, the catalyst was more stable however less reactive when used in the ring closing metathesis reaction. In the same report, the author studied the effect of the bulkiness of the aryl group on the nitrogen atoms. He came to the conclusion that the less bulky the aryl group was, the less stable but more reactive the catalyst was.

Based on these observations, Blechert's group modified Grubbs' initial design and tried to balance between stability and reactivity of the catalyst without affecting the stereoinduction.[16] His concept was to keep the aryl groups of the nitrogen atoms orthogonal to the plane of the imidazole moiety. He believed that the twisting of these groups due to the chiral geometry of the backbone should be responsible for the lack of reactivity of the catalyst. He then decided to have only one asymmetric center on the backbone so that only one aryl group would be twisted. Therefore he could use a much cheaper chiral source: the α-amino acid, L-valine.

While the synthesis of the metal complexes required more steps than the Grubbs one, it had good overall yields (Scheme 1-2). After arylation and reduction of the corresponding N-substituted amino acid to the alcohol, the authors formed a sulfamidate **1-9** in order to open it with boc-mesidine. Deprotection of diamine **1-10** and then cyclization gave imidazolinium **1-11**. The ruthenium complex **1-13** was then obtained as a single isomer by a phosphine displacement in the presence of Hoveyda catalyst **1-12**. In the case of the brominated version, a Suzuki coupling allows access to a more hindered ligand (**1-13c**), before the formation of the imidazolinium.



Scheme 1-2. Synthesis of Blechert's chiral NHC-ruthenium complex

Like Grubbs catalyst, the nitrogen atoms had *ortho*-substituted aryl groups. However, the substituent surprisingly pointed towards the isopropyl group from the L-valine, thus, away from the metal center. Nonetheless, the hindrance caused between the two prevented any rotation of the aryl group hence locking the structure of the catalyst.

Blechert tested his catalysts for the same desymmetrization of diene **1-4** but he didn't obtain as much enantioselectivity as the Grubbs group (66% with **1-13c** vs. 90% with **1-16**). However, he used his own catalysts for the asymmetric ring-opening cross-metathesis (AROCM) of norbornene **1-14** (Figure 1-8). He obtained better results in comparison with the Grubbs group not only in terms of enantioselectivity but also in terms of diastereoselectivity (88% ee, *E*/*Z* ratio: >30/1 with **1-13c** vs. 76% ee, *E*/*Z* ratio: 1/1 with complex **1-16**).[17]

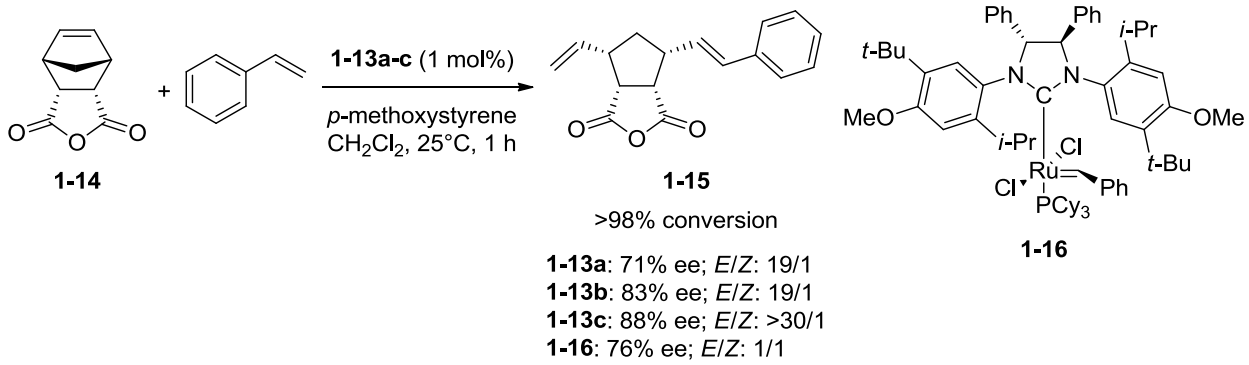


Figure 1-8. Ruthenium-catalyzed AROCM of norbornene **1-14**

In 2008, Shi and co-workers also got inspired from Grubbs design.[18] However, they noticed better enantioselectivity with di-*ortho*-substituted aryl groups rather than monosubstituted ones for the asymmetric diamination of conjugated dienes and triene (Figure 1-9).

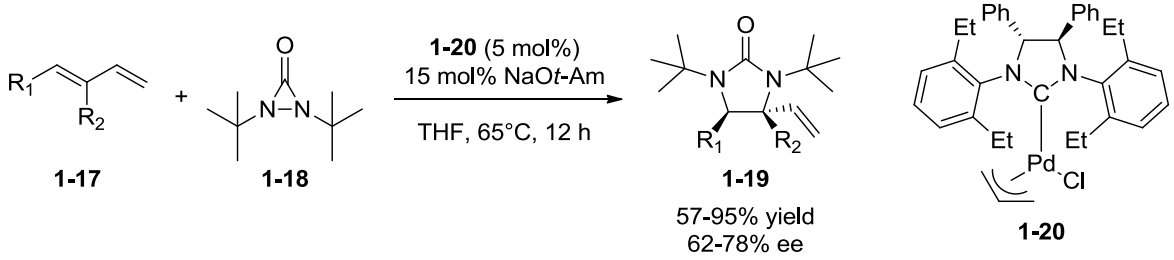


Figure 1-9. Palladium-catalyzed asymmetric diamination of conjugated dienes **1-17**

Dorta and co-workers also used the same chirality on the backbone of the imidazolinium moiety as Grubbs for their own catalyst.[19] However, they replaced the substituted phenyl groups on the nitrogen atoms with 1-naphthyl derivatives to obtain even more hindered ligands. They tested the corresponding palladium catalysts for the intramolecular α-arylation of amides (Figure 1-10). They obtained better enantioselectivity with bulky substituents (3-pentyl) at the 2-position of the naphthyl group.[20] After optimization they were able to form a quaternary center at the benzylic position of a wide variety of 3-allyl oxindoles **1-22**.

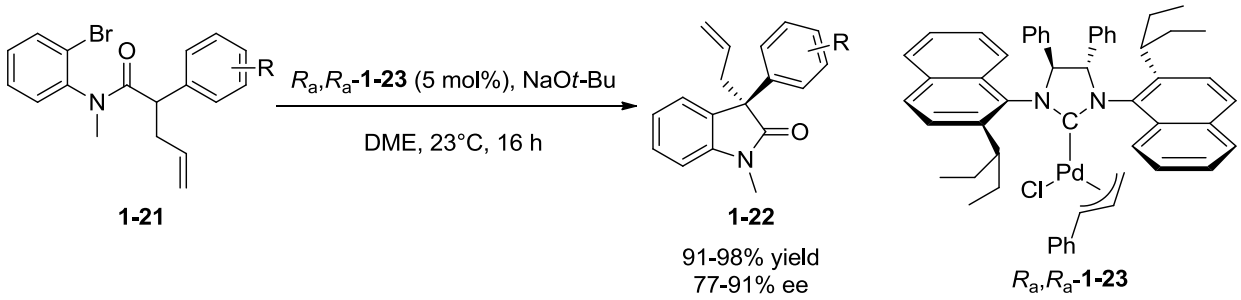


Figure 1-10. Palladium-catalyzed intramolecular α-arylation of amide **1-21**

While the methodology looked attractive, the downside of it was the synthesis of its palladium catalyst. Indeed, the complexation of the free carbene on the metal generated 3 stereoisomers (R_a.R_a-**1-23,** R_a.S_a-**1-23**, and S_a.S_a-**1-23**) that needed to be separated.

Chirality on the Substituent of the Nitrogen Atom

Chirality at the α-position from the nitrogen atom

In 1996, Herrmann was the first one to synthesize a chiral NHC ligand containing the chirality on the nitrogen atom.[21] He condensed enantiopure 1-arylethylamine with glyoxal and formaldehyde to form the corresponding imidazolium **1-24** as a single isomer (Figure 1-11).

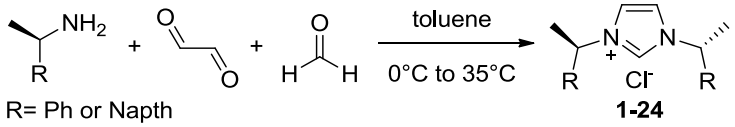


Figure 1-11. Herrmann's preparation of chiral imidazoliums

After deprotonation of the imidazolium, he complexed the corresponding free carbene on rhodium and catalyzed the hydrosilylation of acetophenone with 90% yield and 33% ee (Figure 1-12).

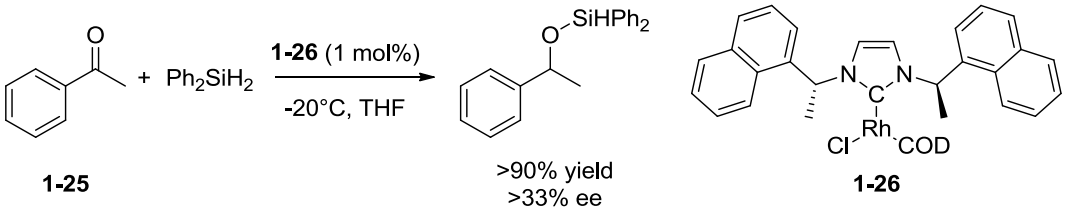


Figure 1-12. Rhodium-catalyzed hydrosilylation of acetophenone **1-25**

In 2011, Czekelius and co-workers got inspired from a different design, but also originally created by Herrmann, to synthesize hindered Au(I) catalysts (Figure 1-13).[22, 23] Because of the linear coordination geometry of Au(I) and the potential *anti*-addition of a nucleophile to the reactive site, a very bulky ligand had to surround the metal center to ensure high enantioselectivity. Herrmann's carbene could have this potential if the phenyl group pointing towards the metal could be further substituted.

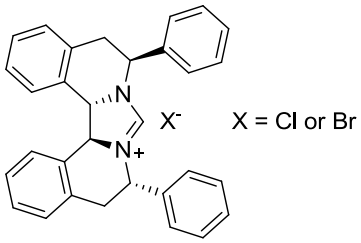
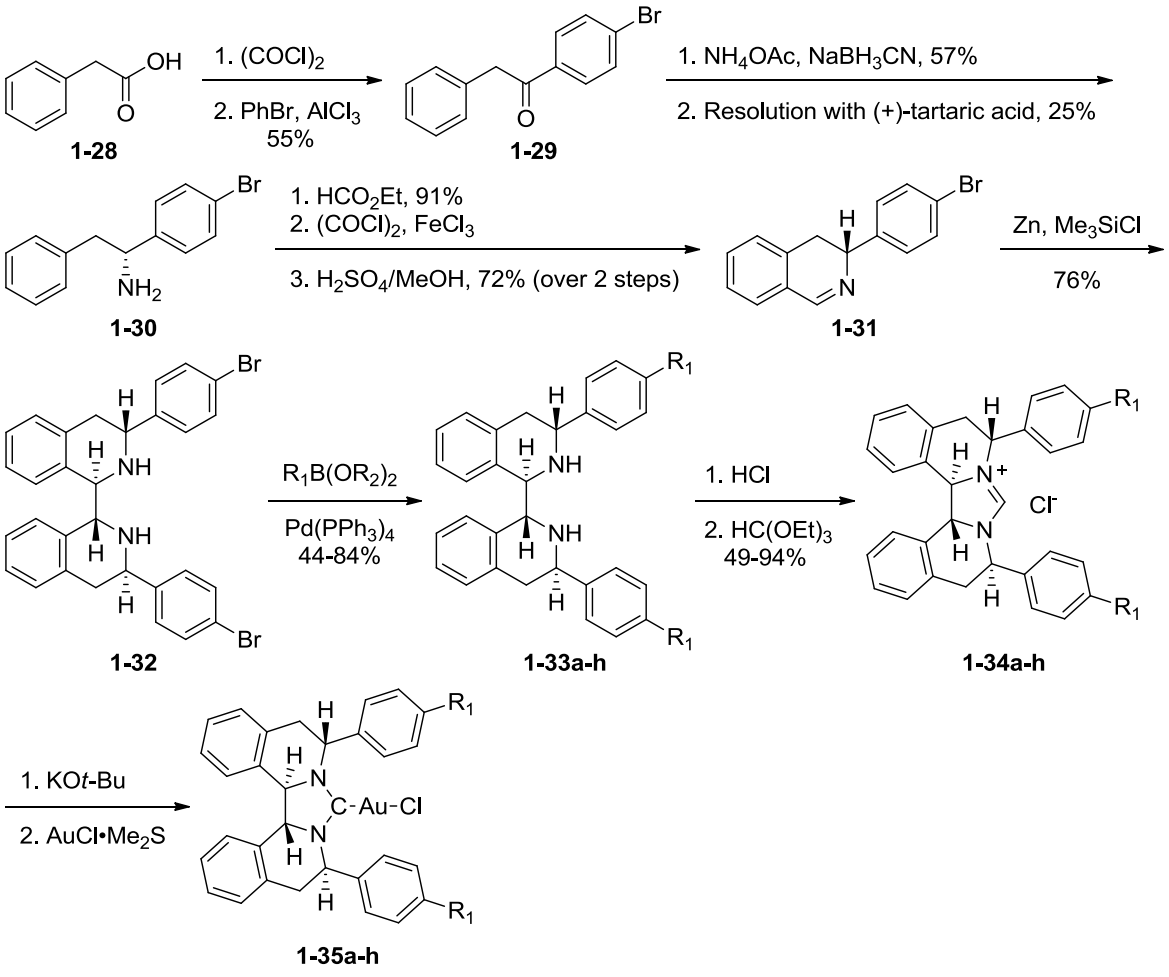


Figure 1-13. Czekelius chiral imidazolinium **1-27**

Czekelius re-visited the original synthesis and used bromobenzene for the Friedel-Crafts acylation in order to perform a Suzuki coupling at a later stage (Scheme 1-3).



Scheme 1-3. Synthesis of Czekelius' chiral NHC-gold complexes **1-32a-h**

Starting from phenylacetic acid **1-28** which was transformed into the corresponding acid chloride, the author performed an arylation with bromobenzene. After reductive amination, the racemic mixture of the amine was resolved with (+)-tartaric acid to obtain the (*R*) enantiomer **1-30**.[24] Then formylation and Bischler-Napieralski cyclization afforded the dihydroisoquinoline **1-31**. Diamine **1-32** was then obtained as a single isomer after reductive dimerization in the presence of zinc and chlorotrimethylsilane. The new concept could now take place by further functionalizing the phenyl pendants with a Suzuki coupling (Figure 1-14). Czekelius was able to get seven new imidazoliniums **1-34**, as carbene precursors, after cyclization with triethyl orthoformate. The corresponding gold complexes **1-35** were obtained by deprotonation of the five-membered ring with potassium *tert*-butoxide and treatment with $AuCl{\cdot}Me_2S$.

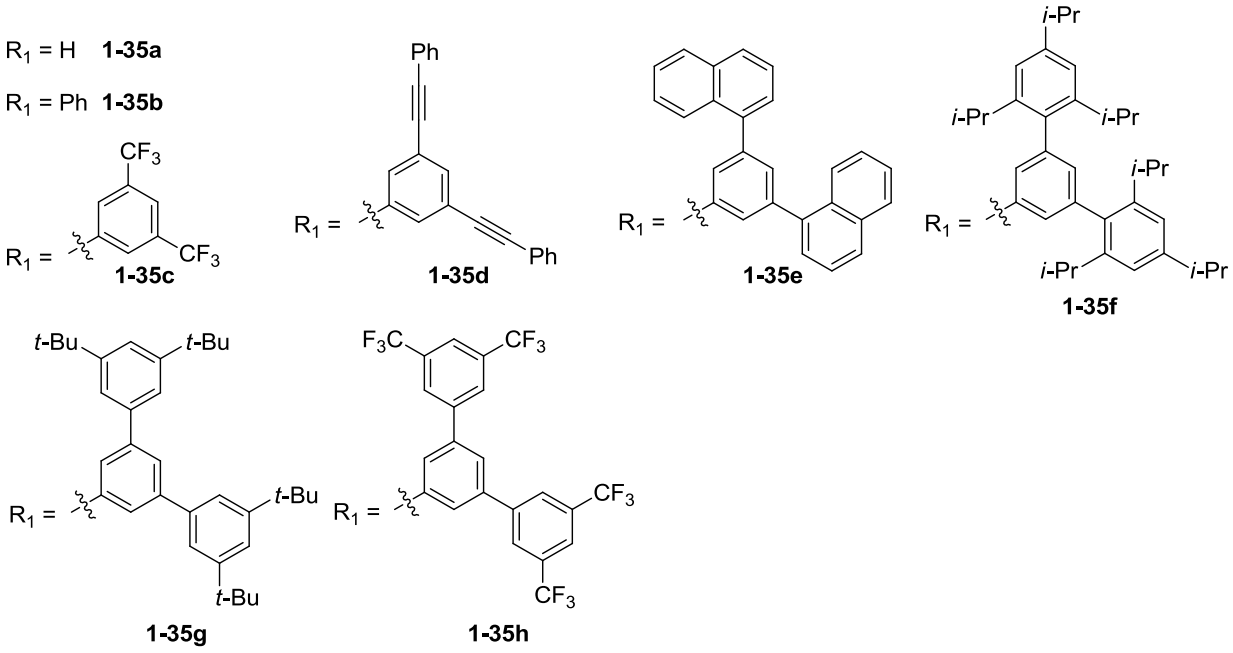
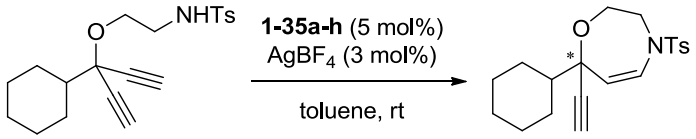


Figure 1-14. Substituent scope of NHC-gold complex **1-35**

With these new highly hindered gold complexes, the authors tested their catalysts in the desymmetrization of diynesulfonamide **1-36** (Table 1-1). They screened all seven

ligands in comparison with Herrmann's one and they found out that indeed bulky substituents improved the discrimination. All of them gave better enantioselectivity than the original ligand (**1-35a**, R_1 = H) with the best candidate being also the most hindered (**1-35f**).

Table 1-1. Ligand scope for the desymmetrization of diynesulfonamide **1-36**



1-36 **1-37**

Entry	Catalyst	Time (h)	Yield (%)	ee (%)
1	**1-35a**	20	53	18
2	**1-35b**	3	traces	22
3	**1-35c**	14	52	45
4	**1-35d**	6	36	34
5	**1-35e**	7	37	39
6	**1-35f**	3	77	51
7	**1-35g**	6	50	30
8	**1-35h**	14	63	40

For Herrmann's group, their challenge was to have optically pure catalysts and easily accessible from cheap chiral sources.[25] He designed new non-chelating NHC ligands based on commercially available chiral starting materials such as (-)-menthylamine or (-)-isopinocampheylamine (Figure 1-15). In only two steps, he could have access to chiral catalysts from these amines. He even came up with substituted cyclic acetals from cheap optically active aminodiols. In the end, he reported five different carbene-rhodium complexes offering a variety of bulkiness.

Herrmann then tested his rhodium complexes on the hydrosilylation of acetophenone **1-25** (Figure 1-16). Only catalyst **1-39** offered some promising enantioselectivity (38%) as the other ones had too much (**1-40**, **1-41**, and **1-42** with their

β-*trans* positioned phenyl groups) or not enough (**1-38**, with its simple methyl groups) hindrance around the metal center, offering poor discrimination.

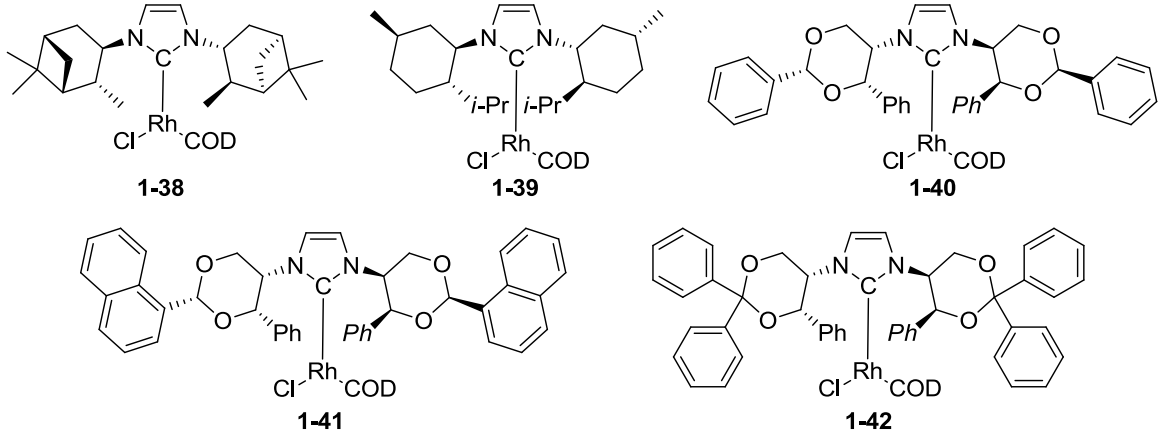


Figure 1-15. Herrmann's rhodium catalysts

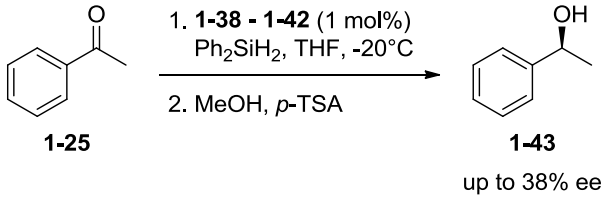


Figure 1-16. Rhodium-catalyzed hydrosilylation of acetophenone **1-25**

However, these complexes being sterically more demanding were more efficient with less bulky substrates such as pyruvic acid esters **1-44** (Figure 1-17). The hydrosilylation of the latter ones gave better results with up to 74% ee.

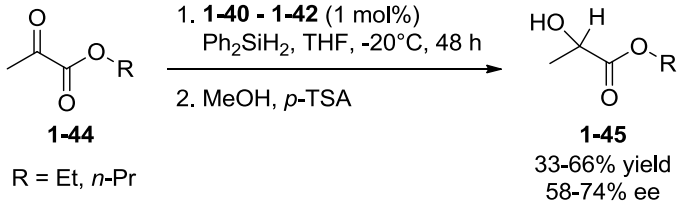


Figure 1-17. Rhodium-catalyzed hydrosilylation of pyruvic acid esters **1-44**

Chirality at the γ-position from the nitrogen atom

For these previously described ligands, the source of chirality was closer to the metal center than the ones having their asymmetric carbons on the backbone. However,

the chiral centers were all either at the α- or β-position (or both) from the nitrogen atoms. Gawley and co-workers wanted to make this center even closer to the metal to increase even more the stereoinduction. In 2011, they were the first ones to report the synthesis of a non-chelating NHC ligand bearing the asymmetric center at the γ position from the nitrogen atom.[26] They complexed their ligand with copper(I) and used the corresponding catalyst in the asymmetric hydrosilylation of acetophenone obtaining 96% ee (Figure 1-18). This C_2-symmetric NHC ligand had two chiral rigid "arms" creating a pocket and thus allowing the approach of the ketone only on its *re*-face to the hydride.

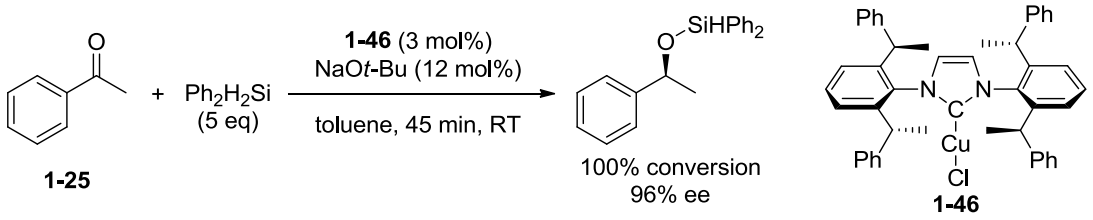


Figure 1-18. Copper-catalyzed hydrosilylation of acetophenone **1-25**

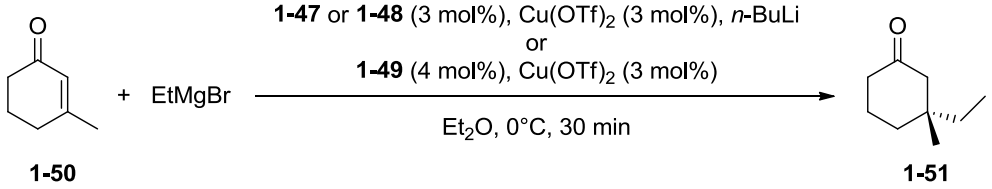
Another way of controlling the enantioselectivity without having a chiral center that close to the metal was to make the catalyst more rigid thus avoiding the rotations around the $C_{carbene}$-metal bond or the nitrogen-substitutent bond. This feature could be accomplished by using a bidentate ligand. In 2010, Alexakis, in collaboration with Mauduit, published a study about copper-catalyzed asymmetric conjugate addition (ACA).[27] While the latter previously reported the synthesis of various chiral bidentate imidazoliniums (**1-49a-f**),[28] the former tested them in the ACA reaction in addition to some C_2-symmetric NHCs (**1-47a-c** and **1-48a-e**) (Table 1-2).

As Alexakis predicted in his study, not only the sterics is important for a good enantioselectivity, but also the chelating effect. Indeed, when he used the non-chelating

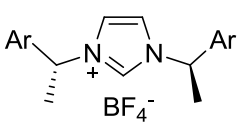
imidazoliums or some of the non-hindered C_2-symmetric imidazoliniums, he saw a poor discrimination (9-42% ee). However, if he increased the steric demand of the N-substitutents or if he used some chelating groups, then the enantioselectivity increased. This effect was then further confirmed when he switched to Mauduit's carbene precursors.

The idea of a bidentate ligand that locked the structure of the corresponding metal complex led Jung and co-workers to develop, in collaboration with Sakaguchi, a tridentate ligand.[29] Their original thought was to make a palladium complex more stable with an increased electronic density around the metal center. Hence, those catalysts would be resistant even in nucleophilic solvents (water, acetonitrile, or alcohols). With three coordination sites from a tridentate ligand, this feature would be accomplished. The authors tested their new new catalysts in the oxidative Heck reaction (Figure 1-19). They obtained very good enantioselectivities (up to 98% ee) but unfortunately with moderate yields (31-61%).

Table 1-2. Carbene precursor scope for the conjugate addition of EtMgBr on enone **1-50**

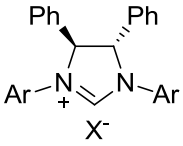
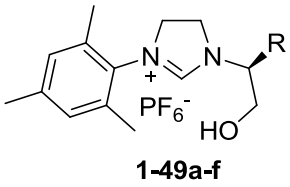


1-50 **1-51**

Entry	Carbene precursor	Conversion	ee (%)
1	 Ar = Ph	81	9
2	1-naphthyl	86	17
3	2-$OMeC_6H_4$	75	42

1-47a-c

Table 1-2. Continued

Entry	Carbene precursor		Conversion	ee (%)
4	 X = Cl, BF_4 **1-48a-e**	Ar = 1-naphthyl	92	68
5		2-naphthyl	82	17
6		2-MeC_6H_4	87	63
7		2-*i*-PrC_6H_4	85	10
8		(8-MeO)-1-naphthyl	>99	67
9	 **1-49a-f**	R = Me	87	68
10		*i*-Pr	91	73
11		*i*-Bu	85	74
12		*t*-Bu	98	80
13		Ph	42	37
14		Bn	78	62

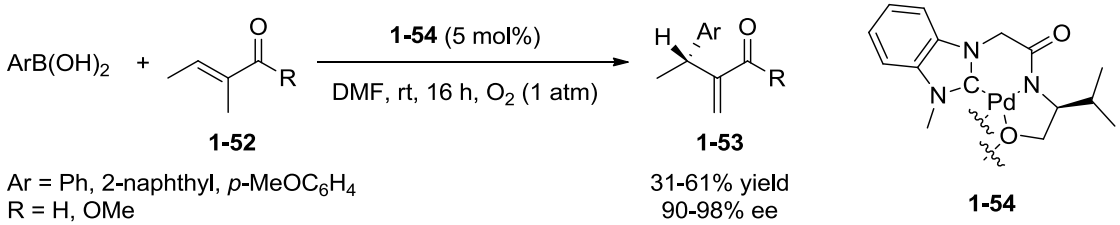
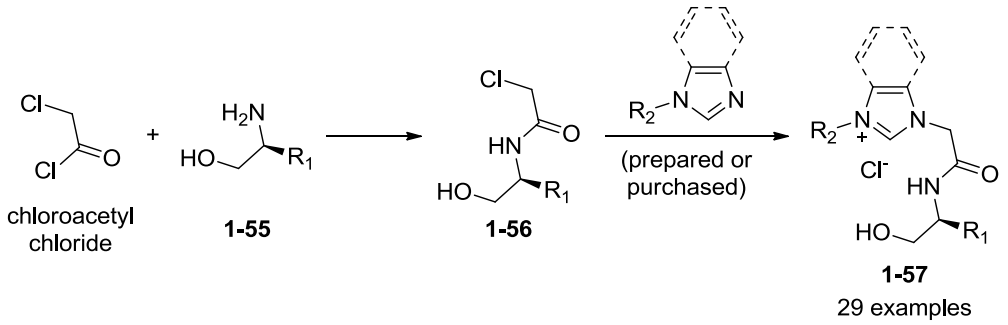


Figure 1-19. Palladium-catalyzed oxidative Heck reaction of enone **1-52**

In 2010, Sakaguchi further developed this design.[30] He tuned the chiral source as well as the non-chiral part (substituent on the nitrogen of the azolium moiety) and was able to obtain a library of tridentate carbene precursors **1-57** (Scheme 1-4). The two-step preparation of these azoliums started with coupling a chiral β-amino alcohol **1-55** with chloroacetyl chloride to give the amide **1-56** which was then aminated with an N-substituted imidazole or benzimidazole.



Scheme 1-4. Synthesis of Sakaguchi's chiral imidazoliums

Sakaguchi tested those new azoliums in the copper-catalyzed conjugate addition of dialkylzinc to cyclic enone. To his great surprise, he was able to obtain either enantiomer of the product with good enantioselectivity with the same chiral ligand (Figure 1-20). Indeed, the copper source used as a pre-catalyst affected the outcome of the selectivity. When the author used $Cu(OTf)_2$ as a copper source, he obtained the opposite enantiomer while using $Cu(acac)_2$ instead.

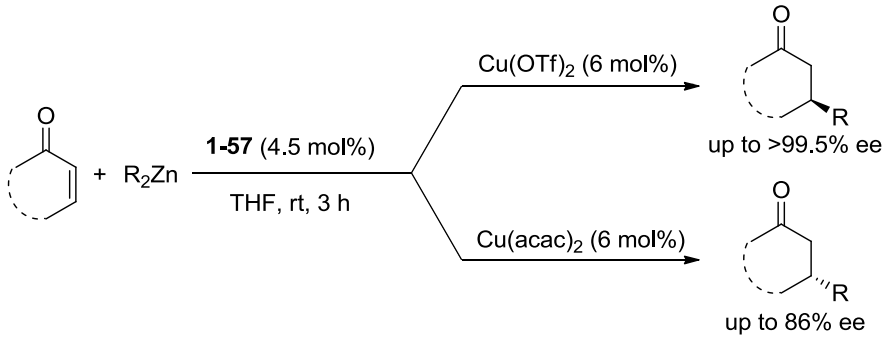


Figure 1-20. Copper-catalyzed conjugate addition of dialkylzinc to cyclic enones

Ligands containing chiral planes

Not all chiral NHC ligands contained an asymmetric atom; they could have chiral planes instead. In 2011, Shi and co-workers reported the synthesis and applications of an optically active NHC gold complex based on a 1,1′-biphenyl scaffold (Figure 1-22).[31] This design was inspired from Hoveyda's work published in 2002 with a binaphthyl

moiety.[32] The ruthenium complex showed excellent enantioselectivity (up to 98% ee) in the asymmetric ring-opening metathesis (AROM) of norbonene **1-14** (Figure 1-21).

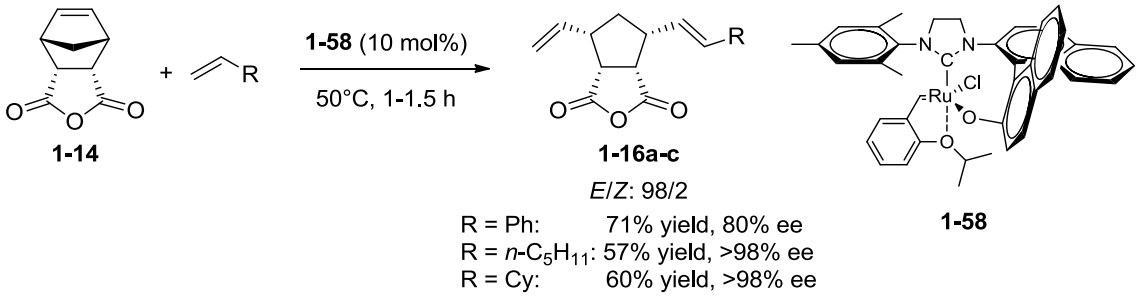


Figure 1-21. Ruthenium-catalyzed AROM of norbonene **1-14**

In the same report, Shi also used a 6,6′-dimethoxybiphenyl system as a chiral plane and tested the corresponding gold complex **1-61** in the intramolecular hydroamination with up to 44% ee (Figure 1-22).

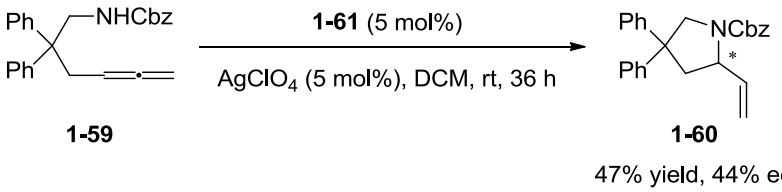
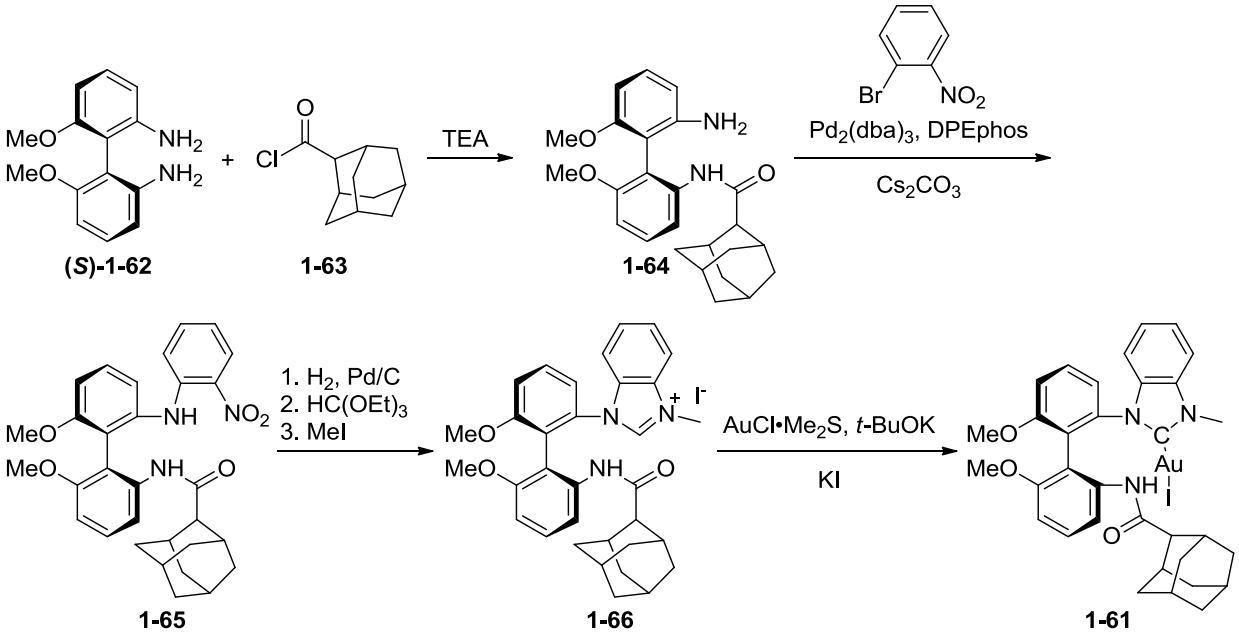
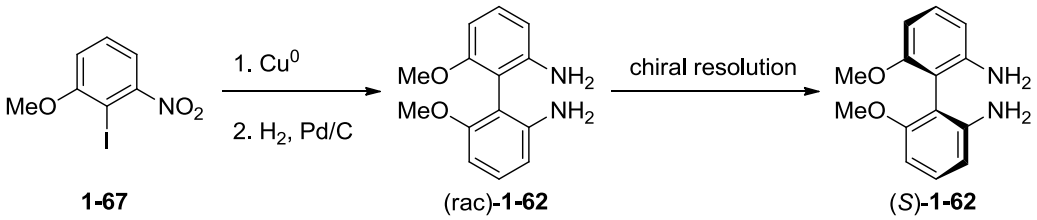


Figure 1-22. Gold-catalyzed intramolecular hydroamination of **1-59**

The preparation of such a catalyst required six steps and even if the overall yield was decent (Scheme 1-5), the chiral starting material **1-62** needed extra steps for its obtention (Scheme 1-6). Indeed,after Ullmann coupling with 2-iodo-3-methoxy-1-nitrobenzene **1-67** in the presence of copper(0), the dinitro compound was reduced to afford a racemic mixture of the corresponding diamine **1-62**. Then a chiral resolution with a tartaric acid derivative was needed to give the (*S*)-isomer.[33]



Scheme 1-5. Synthesis of Shi's chiral NHC-gold complex **1-61**

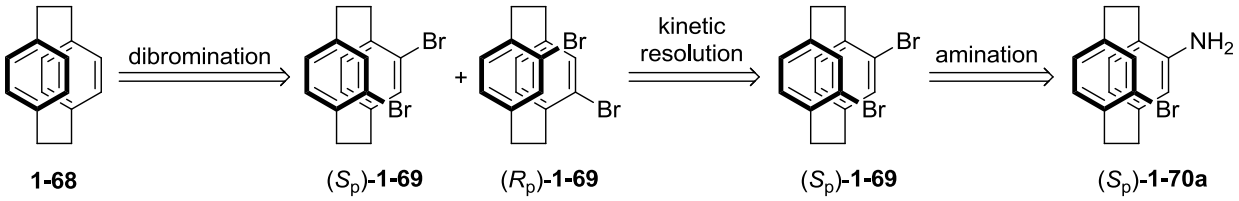


Scheme 1-6. Preparation of enantiopure atropisomer **(*S*)-1-62**

Another kind of chiral NHCs with chiral planes were those based on substituted [2.2]paracyclophanes. Indeed N,N′-disubstituted imidazoliniums exhibited an optical activity with the [2.2]paracyclophanes through chiral planes. This design was originally reported by Andrus in 2003 in collaboration with Ma.[34]

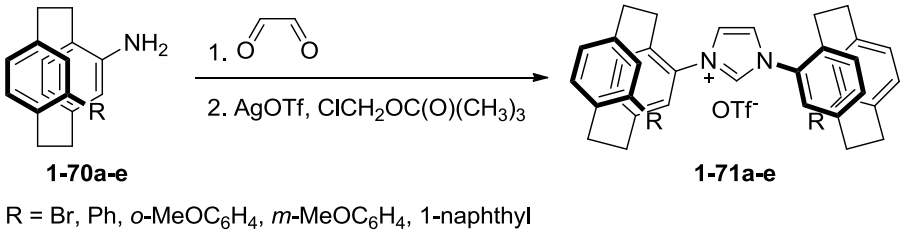
Ma pursued the development of this type of NHCs by switching from imidazoliniums to imidazoliums and by introducing different substituents at different positions on the paracyclophane moiety.[35] The imidazolium version was of a very short access since it required only 2 steps: diimine formation and cyclization (Scheme 1-8). However, the chiral starting material ((S_p)-4-amino-12-bromo[2.2]paracyclophane)

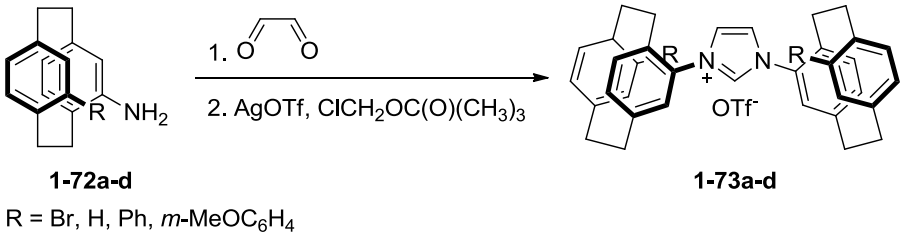
required several steps for its preparation (Scheme 1-7).[36] First, paracyclophane **1-68** was dibrominated to afford a racemic mixture of pseudo-*ortho*-dibromo[2.2]paracyclophane **1-69** which was then kinetically resolved by amination to leave optically pure starting material of the S_p-isomer. Finally, another amination took place by palladium-coupling to obtain the chiral desired compound (S_p)-**1-70**.



Scheme 1-7. Preparation of enantiopure paracyclophane **(S_p)-1-70a**

From this chiral starting material, the bromine atom could further be functionalized with a Suzuki-Miyaura coupling with various arylboronic acids to give pseudo-*ortho*-arylamino[2.2]paracyclophanes **1-70b-e**. Following the same process, as previously described, the author was also able to form diferrent pseudo-*ipso*-arylamino[2.2]paracyclophanes **1-72c,d**.





Scheme 1-8. Synthesis of Ma's chiral imidazolium **1-71a-e** and **1-73a-d**

Ma then tested those new imidazoliums in the rhodium-catalyzed 1,2-addition of arylboronic acids onto benzaldehyde derivatives (Figure 1-23). NHCs were in situ generated after deprotonation of the corresponding imidazoliums with sodium *tert*-butoxide. Carbene precursor **1-71a** was the most promising in terms of enantioselectivity. After optimization, the author got high reactivity with moderate enantioselectivity.

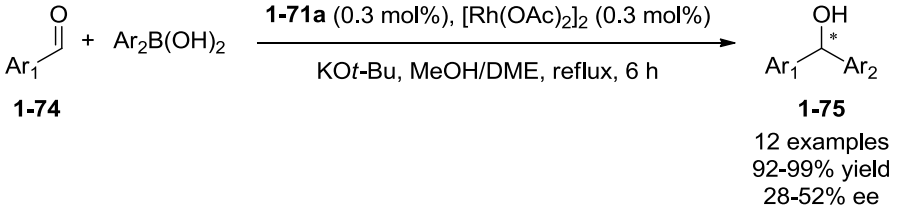


Figure 1-23. Rhodium-catalyzed 1,2-addition of arylboronic acids onto benzaldehyde derivatives

Synthesis of Acyclic Diaminocarbene Ligands

Formation of a Carbene Intermediate

In 1964 Wiberg and Buchler reported the first ADC intermediate formation.[37] They deprotonated formamidinium **1-78** with methyllithium and they isolated the tetraaminoethylene product **1-79** (Figure 1-24). They came to the conclusion that in order to end up with this olefin, the intermediate had to be a carbene. Their reasoning was based on Wanzlick's and Lemal's work who both characterized product **1-77**, obtained after deprotonation of imidazolinium **1-76** (or also called zwitterion).[38] However, none of the groups were able to characterize or isolate the free carbene.

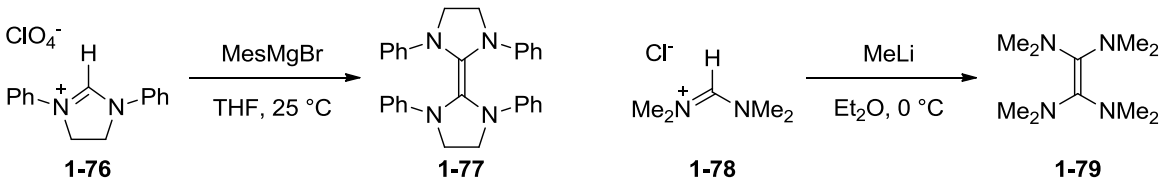


Figure 1-24. Dimerization of imidazolinium **1-76** and formamidinium **1-78**

ADC-Metal Complexes by Functionalization of Isocyanide

Since ADCs seemed to undergo dimerization easily, they couldn't be generated as free species and their precursors had to be complexed on a metal before the carbene generation. In 1969, Richards and co-workers functionalized an isocyanide ligand complexed on platinum by nucleophilic attack of a primary amine to form the first ADC-metal complex ever reported (Figure 1-25).[39] They formed a platinum(II) salt from the reaction between $[PtCl_2(MeNC)(PEt_3)]$ and aniline. This work has been published only a year after the first preparation of an NHC-metal complex.

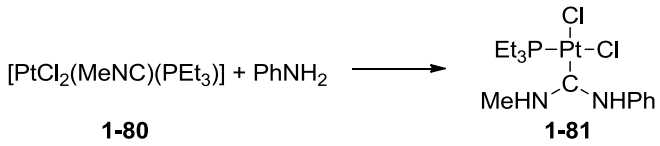


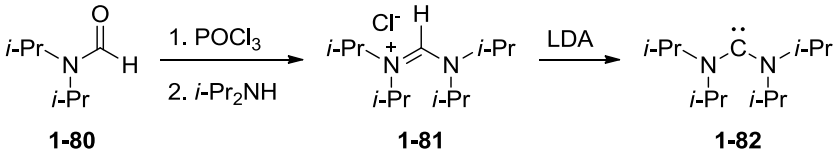
Figure 1-25. First ADC-metal carbene synthesized

From then, different groups in the 1970s used this method to prepare different types of ADC metal complexes.[40, 41] The advantage was to quickly obtain a variety of carbenes, with different electronic and steric properties, by changing the free amine or the isocyanide. However, this route only allowed the use of late transition metals (mercury, gold, platinum, palladium…). Besides the preparation of some of the corresponding isocyanide metal complexes could be tedious.

With those limitations, another way to prepare an ADC metal complex was undertaken. The idea was to isolate the free carbene and then to complex it on a metal. However the challenge of this method was to avoid any dimerization of the free carbene.

First Isolation of a Free ADC

It was Alder who first reported the isolation of a free ADC in 1996.[42] Carbene **1-82** was obtained by deprotonation of the corresponding formamidinium salt with lithium diisopropylamide (Scheme 1-9). Salt **1-81** was synthesized from diisopropylformamide **1-80** with phosphorus oxychloride to form a chloroiminium adduct which was then subjected to a S_N2 type reaction with diisopropylamine. The dimerization of the free entity was prevented due to the steric effect of the isopropyl groups.



Scheme 1-9. Formation of free acyclic diaminocarbene

X-ray analysis of carbene **1-82** showed, as expected, a wider N-C-N angle than its cyclic analogues (121.0° vs. <109°) (Figure 1-26). That wider angle could therefore have the substituents on the nitrogen atoms closer to the metal center, making the complex more stable.

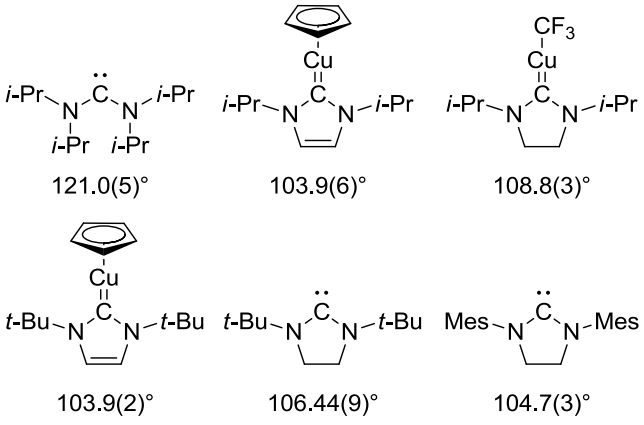


Figure 1-26. N-C-N bond angles of free carbenes and carbene-copper complexes[43-46]

While Alder was able to isolate a free ADC, he quickly realized his method was limited.[47] Indeed, when he applied this procedure to formamidinium **1-83**, he did

observe, by NMR spectroscopy, formation of the corresponding carbene **1-84** but accompanied with the dimerization of the latter giving the ethene product **1-85** (Figure 1-27).

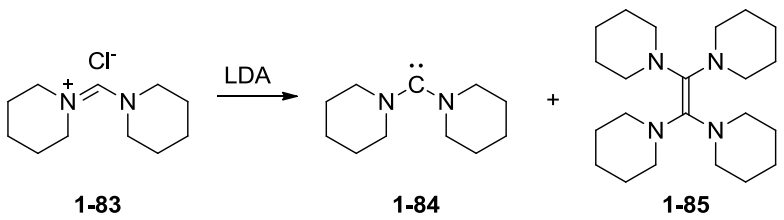
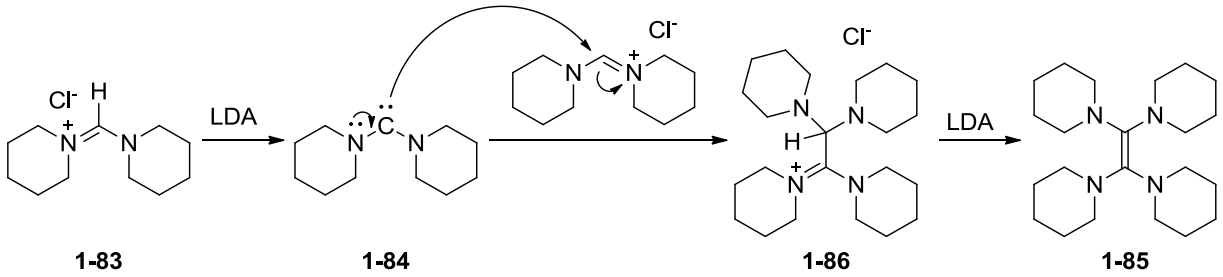


Figure 1-27. Deprotonation of formamidinium **1-83**

Alder proposed this dimerization due to the nucleophilic character of the free carbene. He reported that once carbene **1-84** was formed, it could attack the starting formamidinium **1-83** to give adduct **1-86** (Scheme 1-10). After deprotonation, the corresponding ethene **1-85** was formed. In the case of the tetraisopropylformamidinium, the hindrance of the alkyl groups was too important for the free carbene to attack the chloride salt.

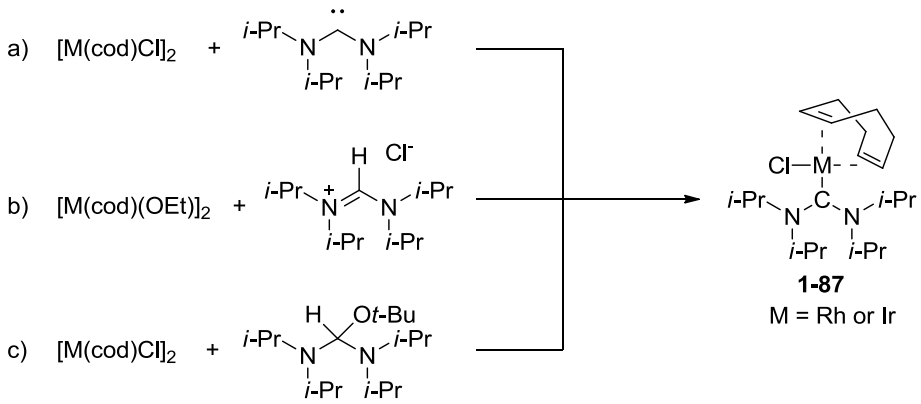


Scheme 1-10. Alder's proposed mechanism for the dimerization of free carbene

ADC-Metal Complexes by Complexation of Free Carbene

In 2002, Herrmann and co-workers reported the first complexation of an ADC on a metal via a free carbene.[48] The authors described several methods to obtain the desired rhodium or iridium complexes. They either isolated the free carbene and complexed it on the metal, or use an internal base coming from the metal or from the carbene

precursor (Scheme 1-11). In the deprotonation case, they generated in situ the free carbene that they complexed on the metal.



Scheme 1-11. Herrmann's preparation of ADC-metal complexes a) with isolated free carbene, b) with EtO-ligand used as a base, and c) by *t*-BuOH removal

According to Herrmann, a simple way to measure the basicity of a carbene was to exchange the cyclooctadiene ligand of the corresponding metal complex with carbon monoxide and to measure the stretching frequency of the C=O bond by IR spectroscopy. He reported that this stretching frequency was directly related to the back donation of the carbene ligand. For example, if a ligand such as an ADC was a weak π-acceptor but a strong σ-donor, then the carbon monoxide (which was a good π-acceptor) would have its back donation increased (Figure 1-28). The anti-bonding molecular orbital of the C=O had a better overlap with the metal d-orbitals. Therefore, the electron enriched anti-bonding made the bond length between the carbon and the oxygen atoms greater. Since the energy of the C=O bond was inversely proportional to its length, hence the longer the bond, the lower the energy (therefore the lower the wavenumber).

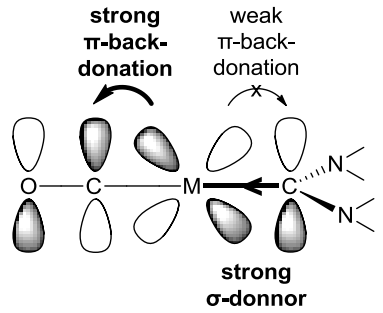


Figure 1-28. π-back-donation of the metal to a C=O ligand

Herrmann measured the C=O stretching frequencies of **1-88** and saw the value was indeed lower than two of its cyclic analogues **1-89** and **1-90** by 19 and 24 cm^{-1}, respectively (Figure 1-29). Therefore, this ADC ligand was more basic (hence more σ donor) than the NHC ones used in the experiment.

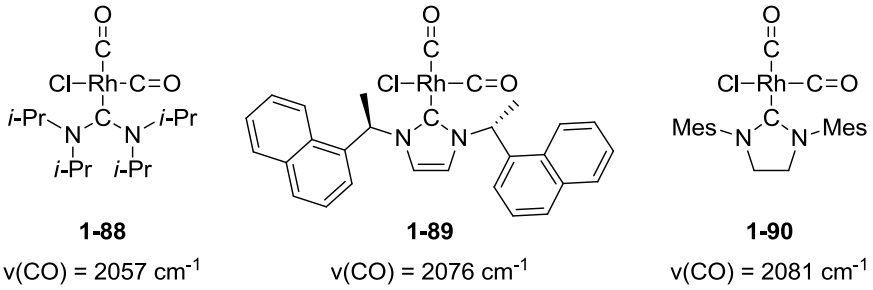
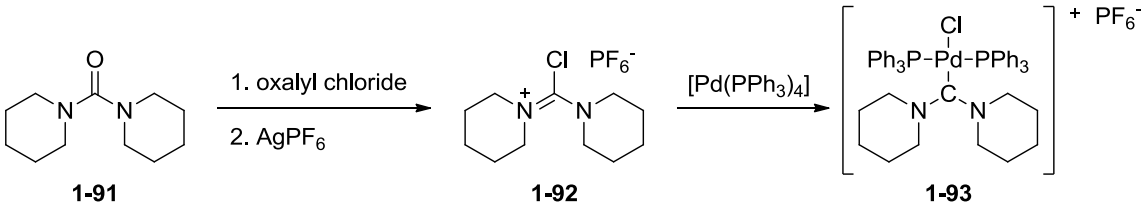


Figure 1-29. Comparison of CO frequencies between ADC- and NHC-Rh complexes

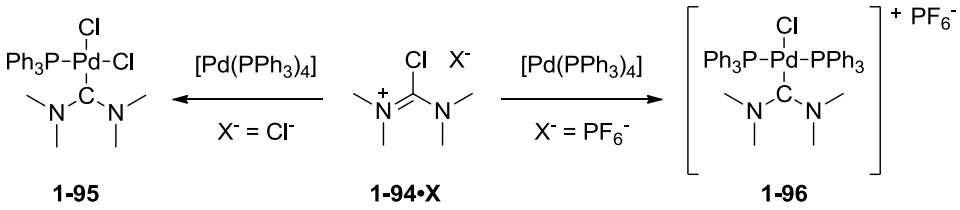
ADC-Metal Complexes by Oxidative Addition

Another alternative to avoid this dimerization drawback was proposed by Fürstner in 2005. He directly complexed the ligand on palladium through oxidative addition of chloroamidinium salt **1-92** with a palladium(0) source (Scheme 1-12).[49] The chloroamidinium can be obtained by oxygen displacement of the corresponding urea **1-91** in the presence of a chlorinating agent (such as oxalyl chloride). The author was then able to obtain the same ADC ligand **1-84** complexed on a metal where Alder failed to isolate the free carbene.



Scheme 1-12. Fürstner's oxidative addition of a chloroamidinium on palladium(0)

With the same method, Fürstner formed the ADC-palladium complex with the least sterically hindered carbene (well known to quickly dimerize) (Scheme 1-13). Moreover, depending on the counter-ion of the chloroamidinium salt, either neutral or cationic metal complex could be prepared (**1-95** and **1-96** respectively).



Scheme 1-13. Preparation of neutral and cationic ADC-palladium complexes

The author tested different ADC-palladium complexes in the Heck reaction obtaining the desired coupled product **1-98** in good yields (Figure 1-30).

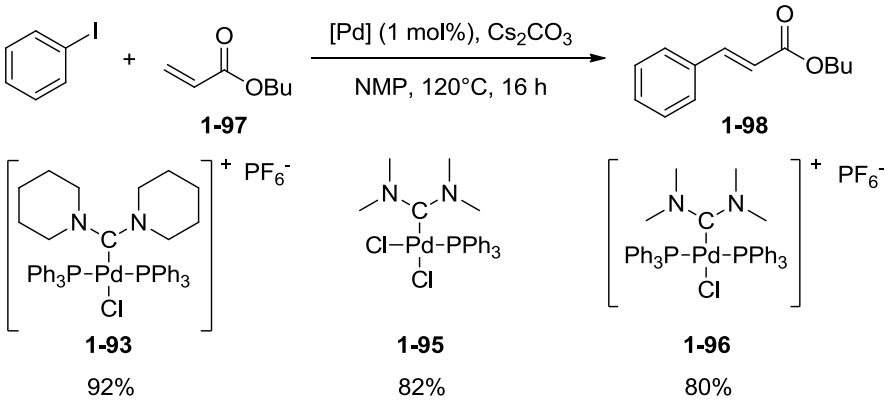
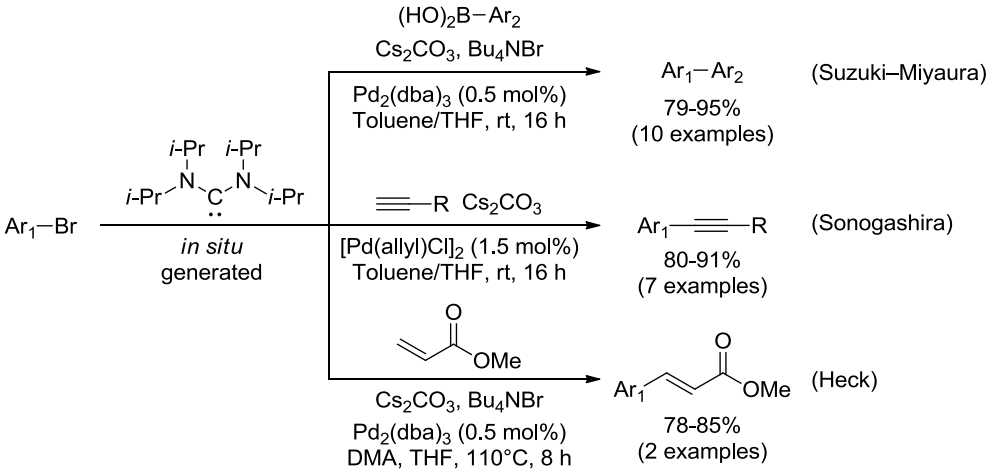


Figure 1-30. Palladium-catalyzed Heck reaction

Applications of ADC-Palladium Complexes in Coupling Reactions

Another breakthrough about the ADC-metal complexes was Thadani's report in 2006.[50] He published the use of in situ generated ADC ligands then complexed on palladium for coupling reactions (Suzuki–Miyaura, Sonogashira, and Heck) in good to excellent yields (Scheme 1-14).



Scheme 1-14. Use of ADC-Pd complexes in coupling reactions

Aryl Substituted ADC-Metal Complexes

Hindered NHC ligands such as IAd, IMes, I*t*Bu, and IPr (Figure 1-31) have been widely used as ligands due to their stability.[51-53] The heavily hindered substituents prevented any possible dimerization. Since the acyclic analogues had a wider N-C-N bond angle, therefore those substituents on the nitrogen atoms should add even more stability to the carbene.

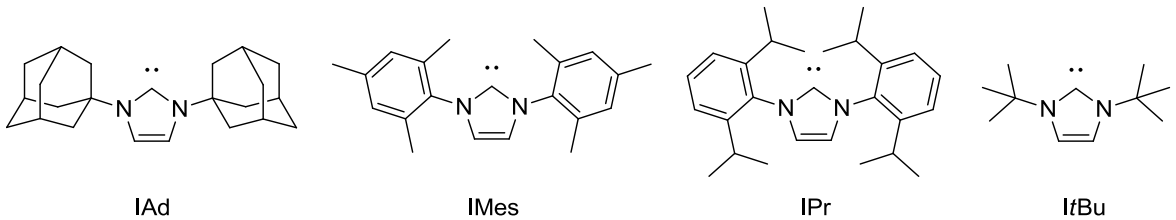


Figure 1-31. Common free NHC ligands

Bielawski and co-workers got inspired from this feature and first reported the synthesis of N,N′-diarylated ADC-metal complexes with the study of their behavior.[54, 55] Since the substitutents on each nitrogen atom were different (one aryl and one alkyl groups) therefore, the geometry of such complexes could adopt different conformations. Indeed, the aryl groups could be both away (*anti*), both close (*syn*), or only one of them close (*amphi*) to the metal center (Figure 1-32).

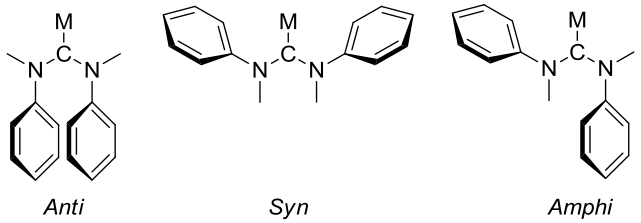


Figure 1-32. Possible conformers of Bielawski's ADC-metal complexes

Initially, the authors thought the aryl groups would adopt the *syn* conformation, thus having the bulky groups the furthest away from each other. However, X-ray structure of rhodium complex **1-99** showed a conformation close to the *amphi* one (Figure 1-33). They postulated this rotation was the most favored due to some CH–π interaction between protons of the methyl group and the π-system of the aryl group. Besides, the 1,3-allylic strain between the substituents on the nitrogen atoms is at its lowest point when the methyl faces the aryl group.

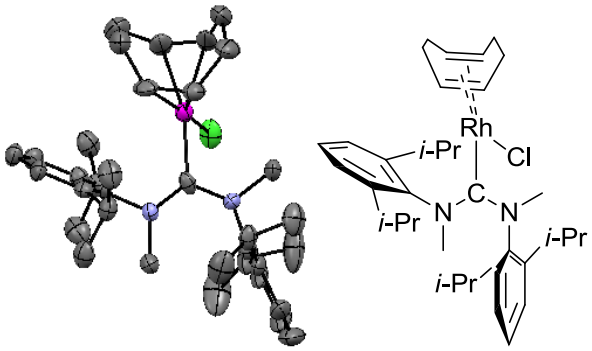


Figure 1-33. X-ray structure of Rh-complex **1-99** in its *amphi*-conformation

Bielawski measured the CO stretching frequency of the corresponding dicarbonylrhodium complex. As expected, the value was higher (v(CO) = 2068 cm^{-1}), meaning the ligand was less σ donor, than the one for **1-88** (v(CO) = 2057 cm^{-1}) which was a tetraalkyl substituted ADC. The aryl groups withdrew the electron density of the nitrogen atoms away from the $C_{carbene}$. However, the carbene was still more donating than the NHC ligands **1-89** and **1-90** ((v(CO) = 2076 cm^{-1}) and (v(CO) = 2081 cm^{-1}) respectively).

Bielawski tested his ADC ligands complexed on ruthenium in the cross metathesis (CM) reactions in comparison with their NHC equivalents (Figure 1-34).

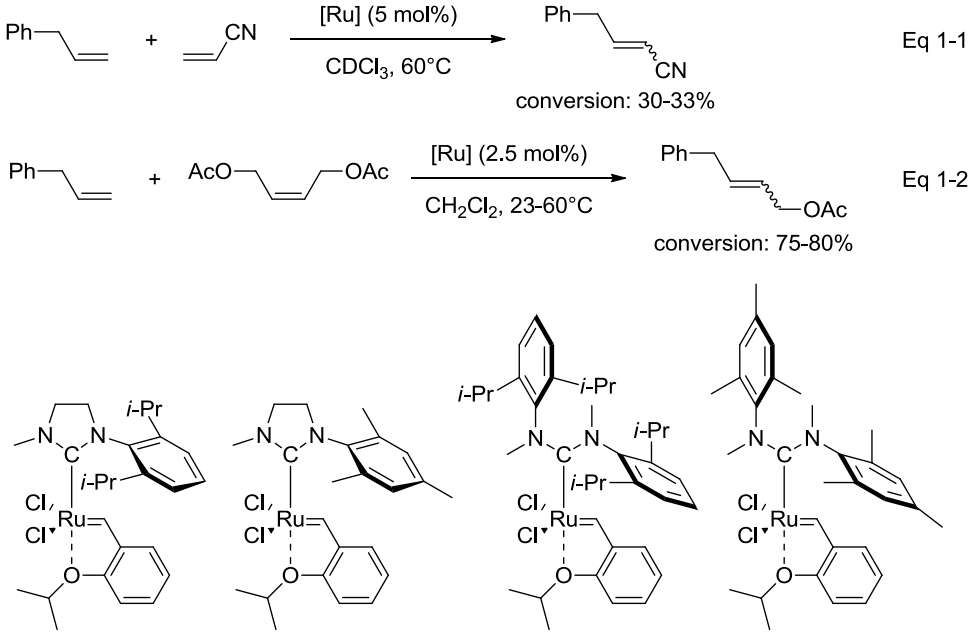


Figure 1-34. Stereoselectivity of Bielawski's ruthenium complexes in cross metathesis

While the ADC-Ru complexes showed some reactivity, they did not have as good discrimination in terms of stereoselectivity as the NHC analogues. The author postulated the increase of sterics of the ADC prevented the isomerization of the CM

product necessary to afford the (*E*)-isomer. Indeed he took an aliquot from a crude mixture after CM reaction with an ADC-Ru complex and he treated it with the NHC-Ru analogue. He observed a change of the ratio in favor of the *E* isomer.

Return to the Original Preparation

Espinet and co-workers came back to the original method of preparing ADC-metal complexes with the functionalization of an isocyanide-metal complex.[56, 57] As seen in Bielawski's work, ADC ligands can adopt different conformations depending on the sterics of the substituents. To avoid this issue, Espinet wanted to lock the structure with some hydrogen bonding. Indeed, in solution or in solid state, he observed that his corresponding hydrogen bond supported heterocyclic carbenes (HBHC) **1-100** showed a preferred conformation due to the hydrogen bonding between the pyridine substituent and the hydrogen of the amine (Figure 1-35).

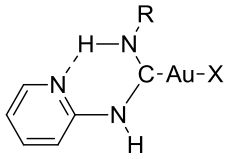


Figure 1-35. Espinet's hydrogen bond supported heterocyclic carbene (HBHC)-gold complex **1-100**

Two years later, Hashmi reported the synthesis of several ADCs (also called NAC: nitrogen acyclic carbene) complexed on gold following the same procedure as Richards in 1969 (Figure 1-36).[58]

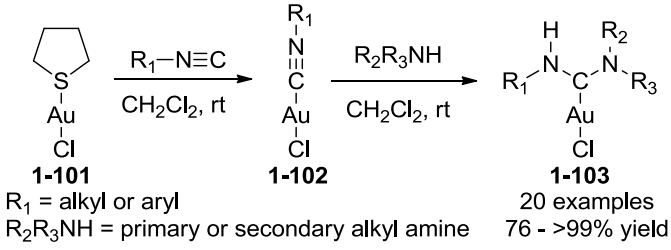


Figure 1-36. Hashmi's preparation of ADC-gold complexes

He obtained a large variety of complexes **1-103** in very good yields. However, this methodology couldn't use any aniline derivatives for the second step as they were not nucleophilic enough to attack the isonitrile moiety **1-102**.

Hashmi reported the same year, an ADC-gold catalyzed tandem reaction forming a tricyclic cage-like structure **1-106** from diol **1-104** and an aniline derivative (or hydrazine derivative) (Figure 1-37).[59]

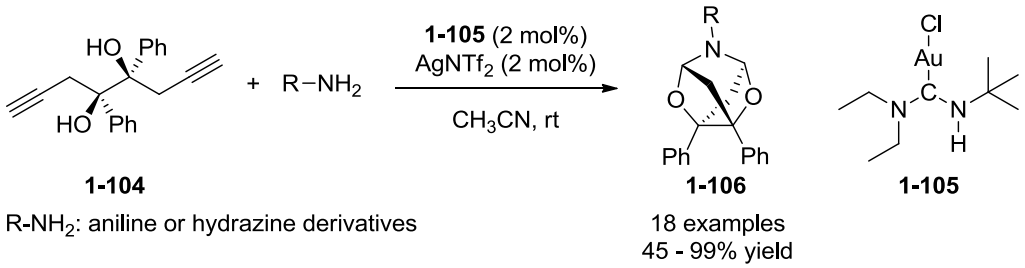
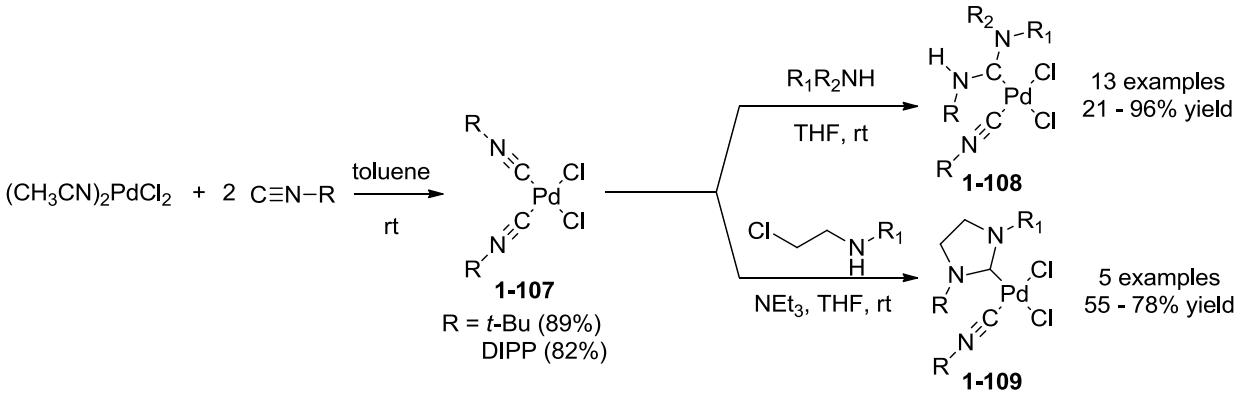


Figure 1-37. ADC-gold catalyzed tandem reaction

In 2011, Hashmi extended this preparation to ADC- and NHC-palladium complexes (**1-108** and **1-109** respectively) with a large variety of substituents on the nitrogen atoms (Scheme 1-15).[60]



Scheme 1-15. Hashmi's preparation of ADC- and NHC-palladium complexes

Then, the author tested the activity of his new complexes in the Suzuki-Miyaura cross coupling reaction (non optimized) (Figure 1-38).

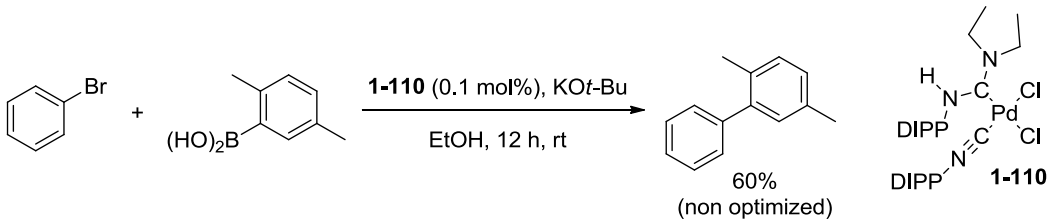


Figure 1-38. Hashmi's complexes in the Suzuki-Miyaura coupling

However, in the same conditions, the NHC-Pd analogue gave greater yield (79%). The author postulated the origin of this better activity might be due to an improved stability and longer catalyst lifetime. Besides, coupling reactions were possible with phenyl chloride in the presence of these complexes while with the ADC-Pd catalyst no desired product was observed.

Chiral Acyclic Diaminocarbene Ligands

Unlike their NHC analogues, chiral ADC ligands can't have their source of chirality on their backbones since they don't have any. Therefore this source must be located on the substituents of the nitrogen atoms. However, because of this lack of backbone, there is a free rotation allowed around the $C_{carbene}$-N bonds which prevents a locked structure (Figure 1-39). Hence, the control of the enantioselectivity is more challenging due to this new degree of freedom.

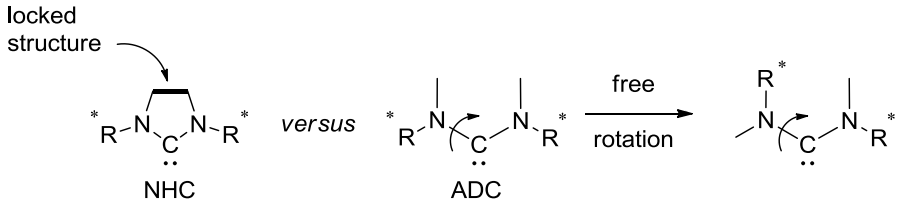


Figure 1-39. The free rotation around the C-N bond allowed for ADC ligands

Very few reports have been published about asymmetric catalysis with chiral ADC-metal complexes.

In 2011, Toste published the asymmetric gold cyclization of phenol-substituted propargyl pivalates **1-111** into chromene derivatives **1-113**.[61] He used BINAM-based chiral ADC ligands, originally designed by Espinet,[57] to obtain the desired products in excellent yields and excellent enantioselectivities (Figure 1-40).

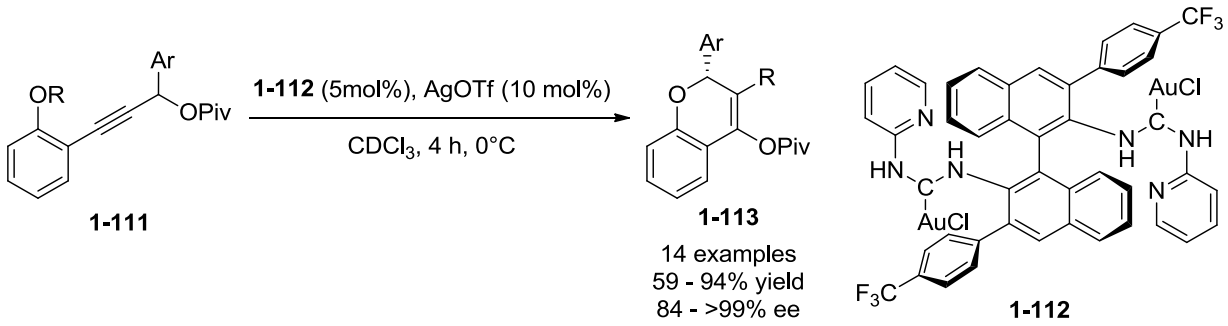


Figure 1-40. Toste's enantioselective gold-catalyzed cyclization of **1-111**

In 2012, Slaughter modified the structure of the previous ligand into a monometallic complex **1-115** and used it for the alkynylbenzaldehyde cyclization (Figure 1-41).[62] He obtained the desired substituted isochromenes **1-116** in good yields and in excellent enantioselectivities.

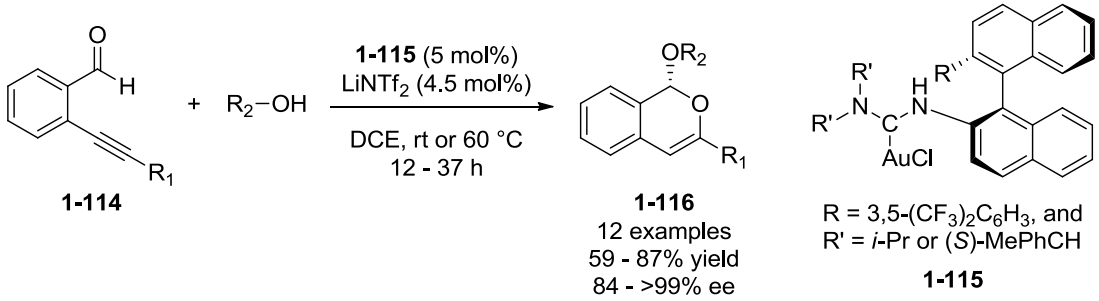
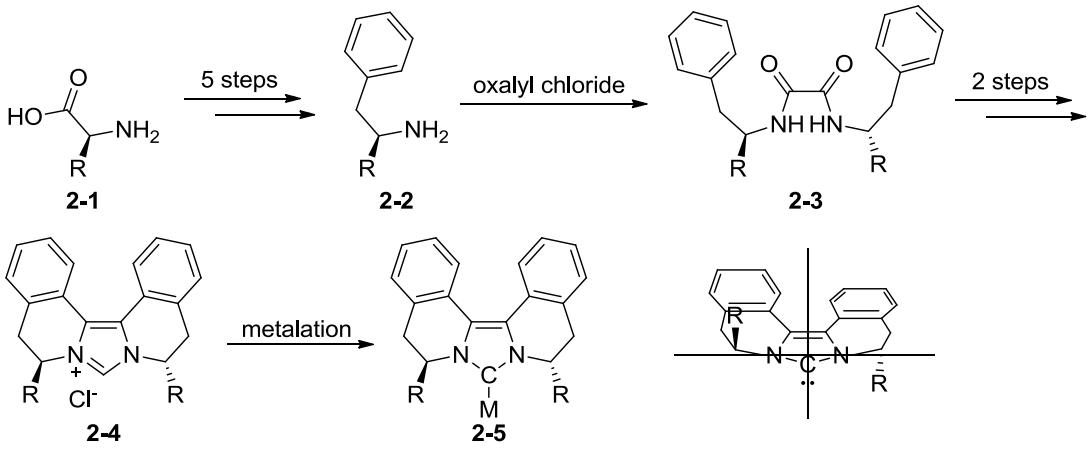


Figure 1-41. Slaughter's enantioselective gold-catalyzed cyclization of **1-114**

CHAPTER 2
DESIGN, SYNTHESIS, AND APPLICATIONS OF CHIRAL N-HETEROCYCLIC CARBENE-METAL COMPLEXES

Previous Designs of Chiral NHC Ligands

In 2008, a new design of chiral NHC ligands was reported by Hong.[63] The biisoquinoline-based carbene contained its chirality α to the nitrogen atom, having an alkyl chain pointing towards the metal sphere. Its preparation was only four steps away from a chiral amine **2-2**, which was derivatized from the corresponding enantiopure amino acid **2-1** (Scheme 2-1). After bisamide **2-3** formation and Bischler-Napieralski cyclization, the bisimine was subjected to another cyclization to form the imidazolium salt **2-4**. Oxidative addition of the heterocycle with silver oxide followed by transmetallation gave the corresponding palladium(II) and copper(I) complexes.



Scheme 2-1. Preparation of Hong's NHC-metal complexes

This new type of complexes have been tested for the asymmetric allylic alkylation with Grignard reagents (Figure 2-1). The catalyst gave a good reactivity along a good regioselectivity (α- vs. γ- product) with a promising enantioselectivity.

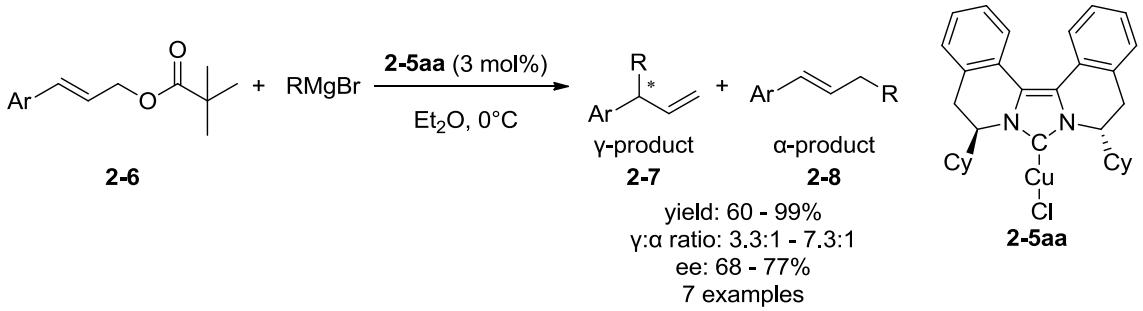
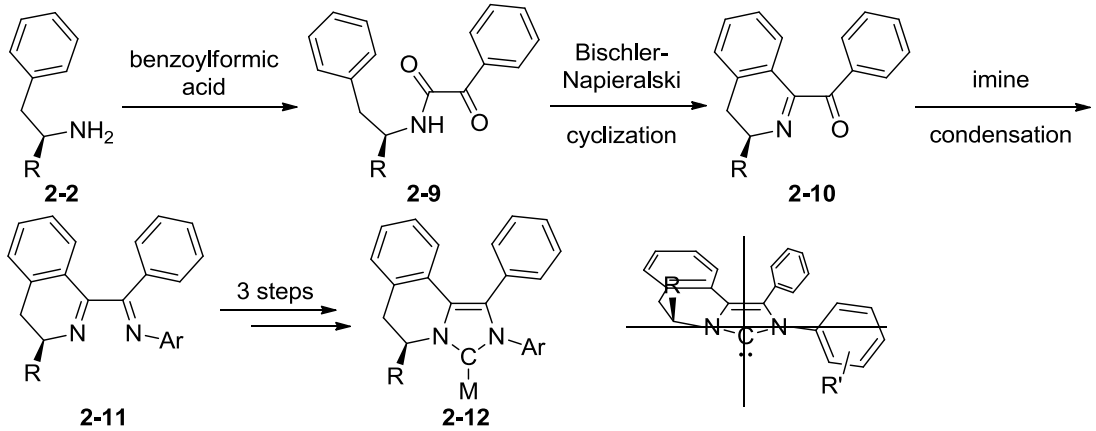


Figure 2-1. Copper-catalyzed allylic alkylation with Hong's NHC-Cu complex

A palladium complex X-ray structure was obtained and showed the C_2-symmetry of the ligand thus blocking two quadrants of the metal coordination sphere.

To further improve the enantio-discrimination, a modification of the original ligand has been designed. Blocking three quadrants this time, the C_1-symmetric monoisoquinoline-based carbene was synthesized and reported in 2010.[64] The chirality part still came from the same series of amines (which came from the enantiopure amino acids). However, instead of coupling it with oxalyl chloride to form the corresponding bisamide, it was treated with benzoylformic acid to give an α-ketoamide **2-9** (Scheme 2-2).



Scheme 2-2. Preparation of Hong's C_1-symmetric NHC ligands and their metal complexes

After Bischler-Napieralski cyclization and imine condensation, the new bisimine **2-11** was then cyclized. Transmetallation as previously described was finally performed to obtain the C_1-symmetric NHC-metal complex **2-12**.

For the imine formation, a bulky aniline derivative was used to block the two quadrants on the right side of the complex. Since this condensation occurred at a late stage of the NHC synthesis, it was easy to tune the hindrance (as well as the electronic effects) the aromatic substituent could offer.

An X-ray structure for the gold complex showed indeed three quadrants being blocked by the chiral source and by the aniline derivative.

These C_1-symmetric ligands showed a good enantioselectivity in the β-borylation of acyclic α,β-unsaturated amides **2-13** (Figure 2-2).

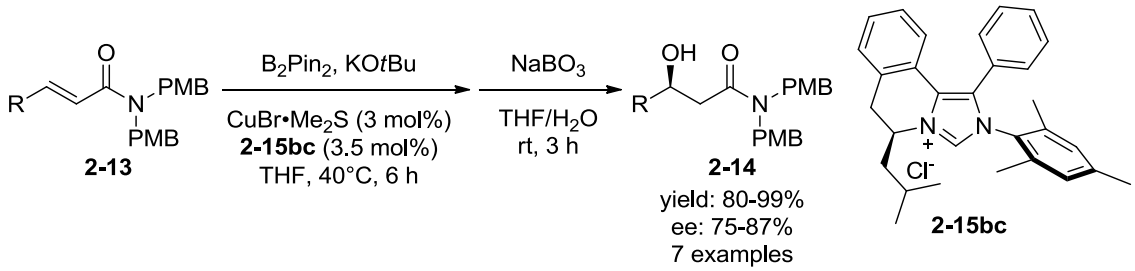
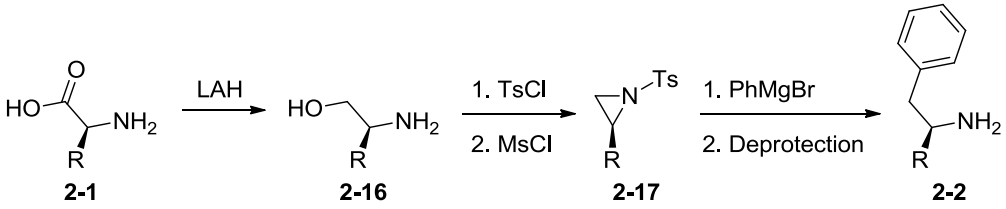


Figure 2-2. Copper-catalyzed β-borylation with Hong's C_1-symmetric NHC

The source of chirality for both C_2- and C_1-symmetric ligands was from the amino acids. Therefore it was possible to obtain both enantiomers and to tune the R substituent depending on the starting material used. Also, since none of the transformations throughout the different syntheses epimerized any intermediates, then the carbenes were of high enantiopurity. However, the availability of the R substituent was dependent on the availability of the amino acids. Moreover, the synthesis called for

the chiral source from the very first step. It was therefore difficult to extend the scope of the ligand.

The design had to be rethought so that more R substituents could be included in the scope with different electronic and steric effects. To see how to improve this feature, it was important to understand how the chiral free amine was prepared. First, the amino acid **2-1** was reduced to the amino alcohol **2-16** (Scheme 2-3). The hydroxyl group was then activated for an intramolecular S_N2 reaction with the N-Ts protected amine to form the corresponding azide **2-17**. Next, the three-membered ring was opened with phenylmagnesium bromide as the source of the benzene ring in the isoquinoline. Finally, the free amine **2-2** was obtained after N-Ts cleavage in the presence of lithium.



Scheme 2-3. Preparation of the chiral free amine **2-2**

Overall, the chiral amine, used for the preparation of C_1- and C_2-symmetric ligands, was derivatized from an amino acid and from phenylmagnesium bromide. The natural starting material was the source of the chirality while the Grignard reagent was a building block for the isoquinoline moiety (Figure 2-3).

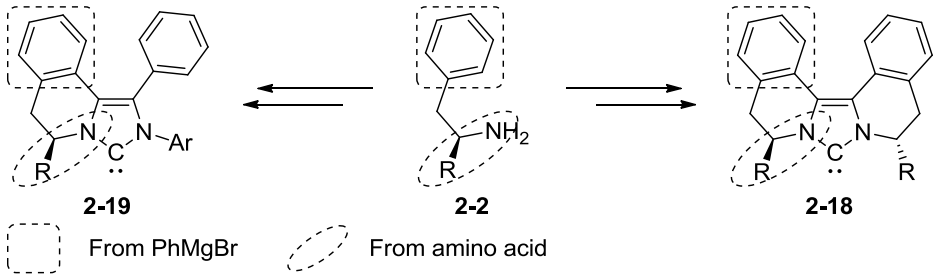


Figure 2-3. Origin of the chiral isoquinoline moiety for C_1- and C_2-symmetric ligands

Improvement of the Original Design

Upon closer look at the chiral free amine, another similar preparation could also be suggested. Indeed, the structure of phenylalanine could be recognized with an R substituent at the α-position (Figure 2-4). Therefore, the benzene ring for the isoquinoline could come from phenylalanine also responsible for the source of chirality. Besides, the R substituent could come from an organometallic reagent.

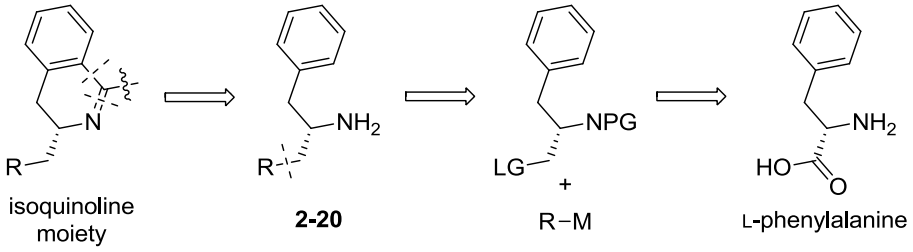
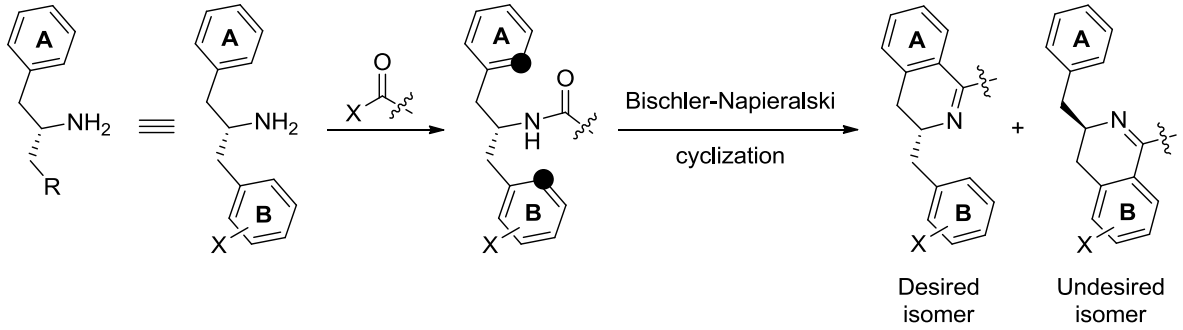


Figure 2-4. Retrosynthesis for the preparation of the chiral isoquinoline moiety

With this new design, the scope would find a great extension. Moreover, this preparation would still benefit from the original pathway that is to say allowing the access to both enantiomers and no possible epimerization of the chiral center. Last, the aziridine intermediate would be the common starting point for all the different carbene precursors allowing the steric and electronic variations at the next stage (attack of the organometallic reagent). Therefore, it would only require two steps: ring opening and deprotection to obtain the free amine, common synthon for the C_1- and C_2-symmetric carbene syntheses.

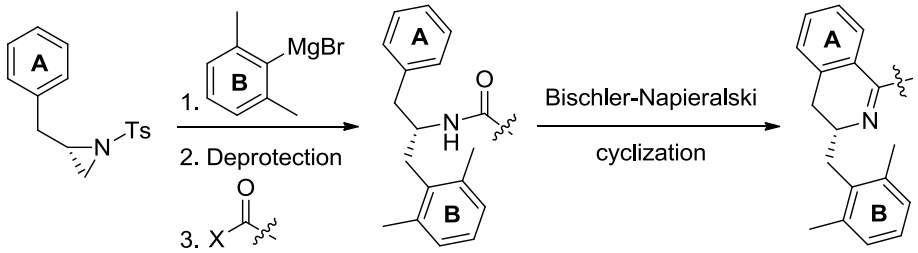
The original idea of an R scope was to increase its steric demand. Therefore the attention went to phenyl derivatives. However, a careful choice was important to make, keeping in mind that it had to be compatible with the subsequent steps to the aziridine formation. For example, the Bischler-Napieralski cyclization called for a ring formation with the nitrogen atom and the *ortho*-position of the benzyl group (Scheme 2-4). If the R

group had such a carbon available, then a competition would occur and would give two different structural isomers.



Scheme 2-4. Formation of structural isomers after Bischler-Napieralski cyclization

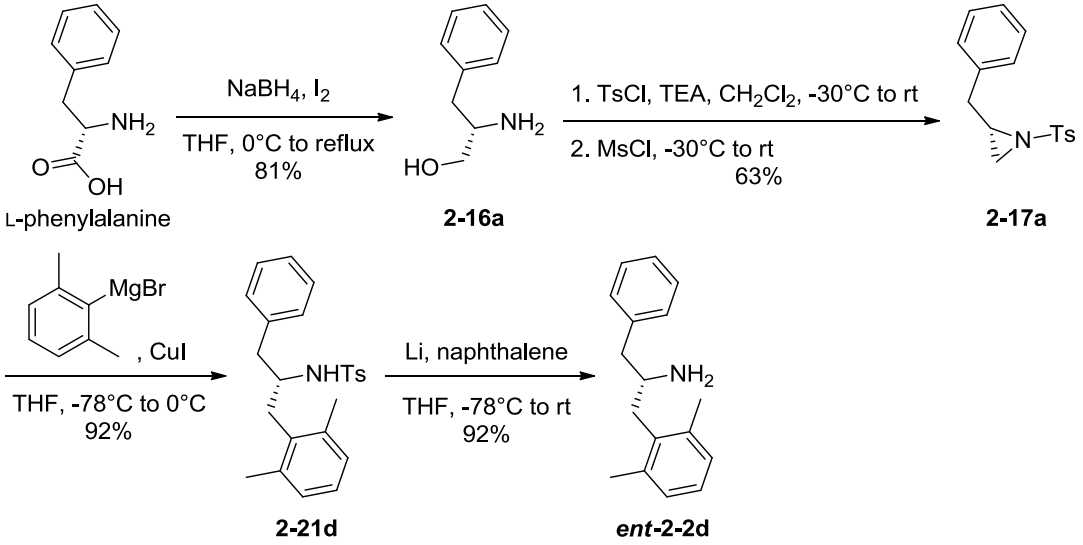
To avoid such an issue, ring **B** would have to be substituted on both *ortho*-positions so that ring **A** only would cyclize with the amide moiety. One of the commercially available Grignard reagents solving this problem was the 2,6-dimethylphenylmagnesium bromide. Hence, the two methyl groups would not only increase the hindrance but they would also block the *ortho*-positions of ring **B** (Scheme 2-5).



Scheme 2-5. New target for the chiral isoquinoline moiety

The synthesis started with the reduction of L-phenylalanine to L-phenylalaninol **2-16a** using standard conditions (Scheme 2-6).[65] Then, the aziridine **2-17a** was formed with the same procedure as previously described. Next, the Grignard reagent was activated with an equivalent of copper(I) iodide to generate the corresponding

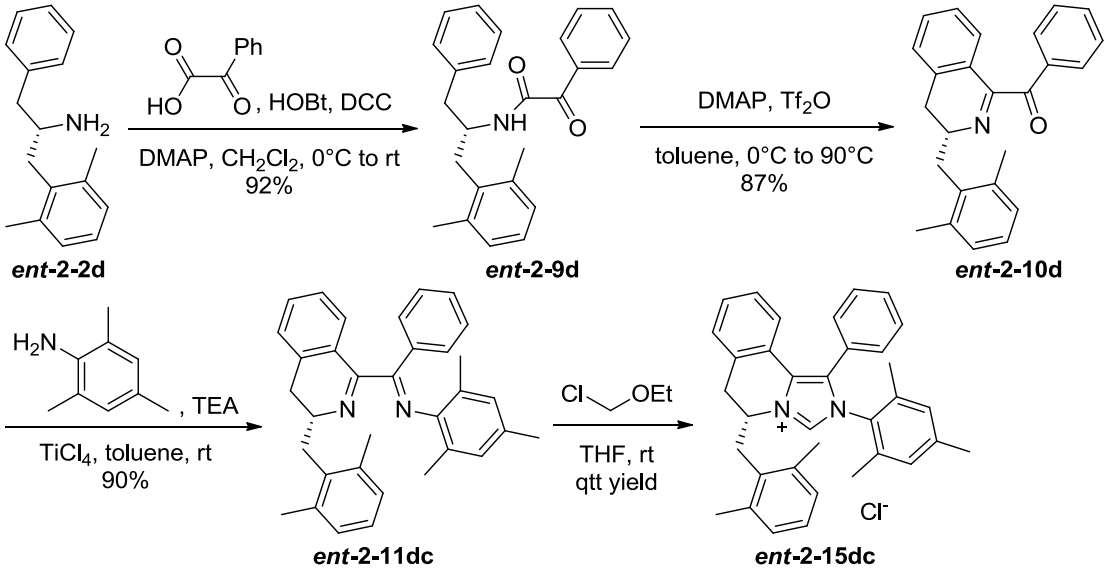
organocopper compound before addition of the aziridine. The free amine ***ent*-2-2d** was obtained by tosyl group removal with lithium.



Scheme 2-6. Preparation of amine ***ent*-2-2d**

Synthesis of the New C_1-Symmetric Carbene Ligand

The free amine ***ent*-2-2d** was first subjected to keto-amide formation in the presence of benzoylformic acid (Scheme 2-7).



Scheme 2-7. Formation of imidazolium ***ent*-2-15dc**

After Bischler-Napieralski cyclization, the imine ***ent*-2-11dc** was then obtained by condensation of the carbonyl compound ***ent*-2-10d** with mesidine. Finally, another cyclization with chloromethyl ethyl ether afforded imidazolium ***ent*-2-15dc** as a carbene precursor.

Applications of the New C_1-Symmetric NHC Ligand

With this new ligand precursor in hand, it was interesting to test its potential activity and enantioselectivity. An interesting reaction to have a look at was the 1,2-addition reaction. Miyaura published the first rhodium-catalyzed 1,2-addition to carbonyl derivatives in 1998 (Figure 2-5).[66] He also reported the use of a chiral ligand ((*S*)-MeO-MOP), designed by Hayashi,[67] for the asymmetric version. He obtained the diaryl alcohol in 41% ee and 78% yield.

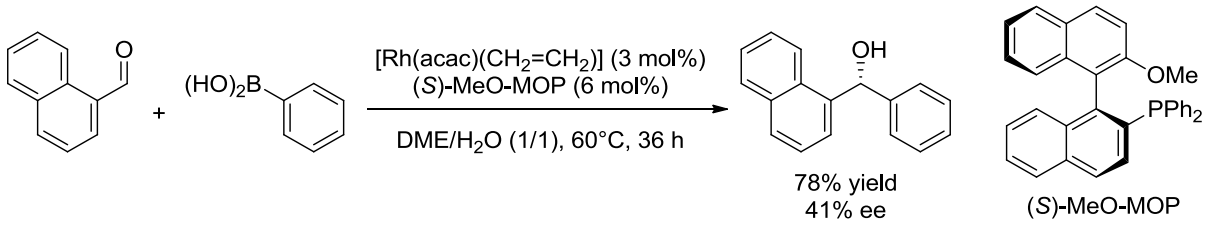


Figure 2-5. First rhodium-catalyzed 1,2-addition

From then, different research groups improved the selectivity with various ligands (phosphoramidites,[68] spirophosphites,[69] bicyclic dienes,[70, 71] or other chiral phosphines[72]) and metals (zinc,[73] palladium,[74] or iron[75]). While high enantioselectivities were obtained with phosphines, carbene ligands didn't give the same outcomes. In 2005, Bolm reported an encouraging result with one of his [2.2]paracyclophane-containing imidazoliums as NHC precursors (Figure 2-6).[76]

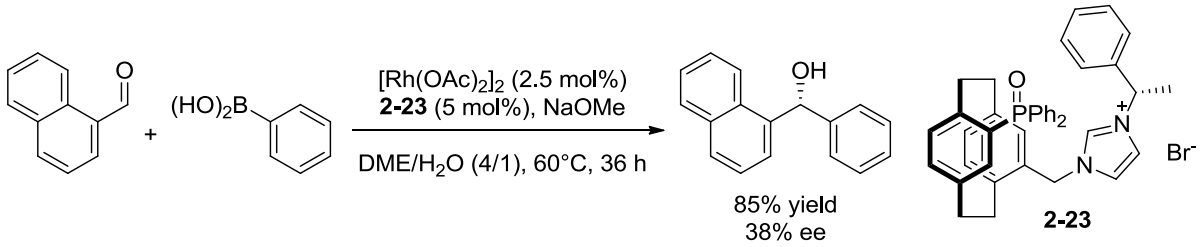


Figure 2-6. NHC-rhodium catalyzed asymmetric 1,2-addition

For several years, this result was considered as the milestone for the asymmetric 1,2-addition with carbene ligands, until two reports were published independently in 2010. First, Ma obtained the diaryl alcohol in a rhodium-catalyzed system with his C_2-symmetric imidazoliums as previously discussed (Figure 2-7).[35]

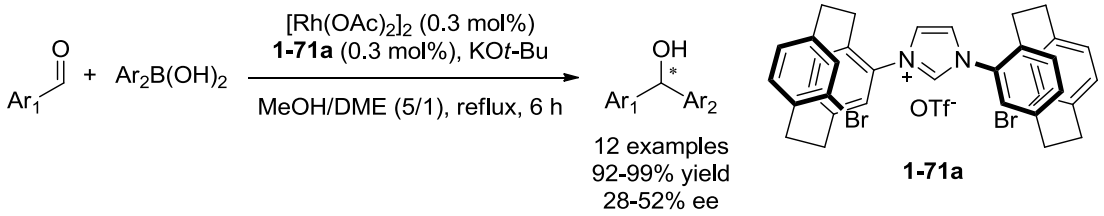


Figure 2-7. Ma's NHC as ligand for asymmetric the 1,2-addition

The same year, Shi reported the use of bis(carbene)-palladium complexes catalyzing the 1,2-addition in moderate to good yields and in slightly higher enantioselectivity (Figure 2-8).[77]

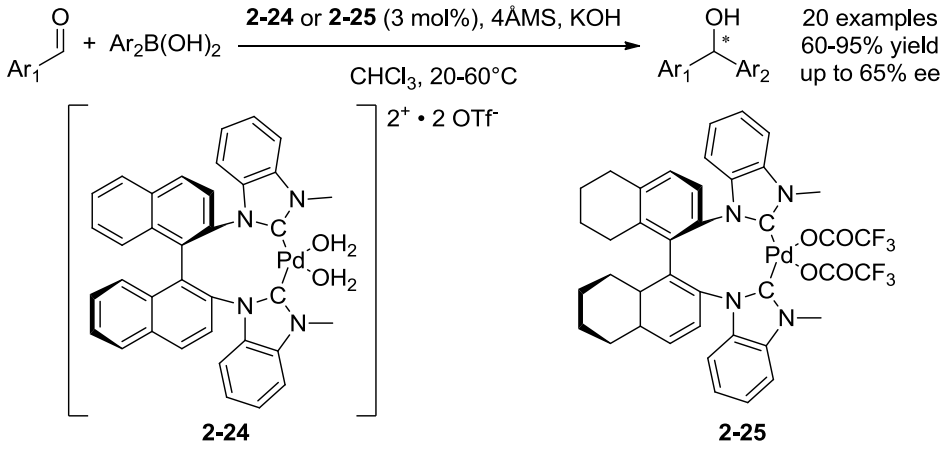


Figure 2-8. Shi's bis(carbene)-Pd complexes in the asymmetric 1,2-addition

Also, another study from Ding and Wu in 2008 showed the 1,2-addition could also be catalyzed by a copper(II) source in the presence of electron rich or bidentate phosphines (PAr_3, BINAP, dppb, or dppf) (Figure 2-9).[78] There were several advantages for using copper as a catalyst over palladium. Not only the price but also the functional group tolerance were of interest. Indeed, the brominated or formylated substrates were not suitable for the arylation with palladium catalysts.

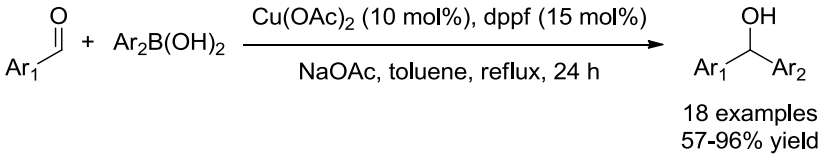
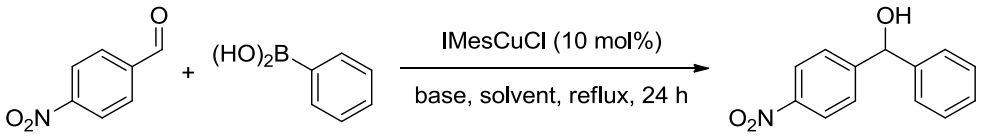


Figure 2-9. Copper-catalyzed 1,2-addition

Since there was still room for improvement in the enantioselectivity and the fact that the reaction could be catalyzed by a copper source, it was very encouraging to test the newly synthesized ligands.

Before testing chiral ligands, it was important to know whether the reaction could take place in the presence of a carbene instead of a phosphine. Using the same conditions as Ding and Wu's, it was nice to see the product could be obtained in moderate yield with isolated IMesCuCl (Table 2-1, entry 1). A base (entries 2-5) and a solvent (entries 6-8) scopes were then performed to optimize the yield but unfortunately without any success. It seemed a mild organic base would suit better than an inorganic (entries 2-4) or a stronger (entry 5) base. The reaction might need high boiling point solvent to process as in THF no reaction was observed (entry 6). However, polar media such as DMF or nitroethane gave decomposition (entries 7 and 8).

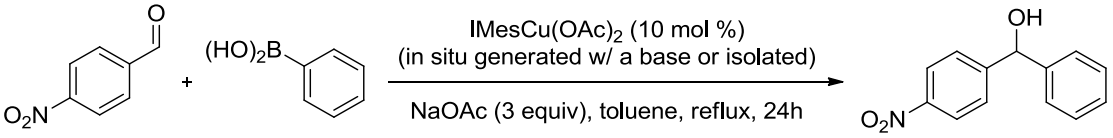
Table 2-1. Optimization of the reaction conditions



Entry	Solvent	Base	Yield (%)
1	toluene	NaOAc	46
2	toluene	KOH	<7
3	toluene	LiOH	<5
4	toluene	CsF	29
5	toluene	KO*t*-Bu	10
6	THF	NaOAc	No reaction
7	DMF	NaOAc	decomposition
8	$EtNO_2$	NaOAc	decomposition

The oxidation state of the copper source was then screened. While carbene-copper(I) complexes could be easily obtained – either by oxidation in the presence of silver oxide and then transmetalation or by generation of the free carbene with a base and complexation on a metal – the copper(II) analogues were more tedious to prepare. It has been reported that NHC-Cu(II) complexes were more stable with at least one O-chelating ligand (OAc, OAlkyl) than halides.[79] Besides, their formations were not possible to monitor by ^{1}H NMR analyses as they were paramagnetic species. Moreover, they were not stable enough to be purified by column chromatography. However, the preparation of IPrCu(OAc)$_2$ has been reported via complexation of the free carbene on the copper(II) diacetate.[80] Therefore, IMesCu(OAc)$_2$.was then prepared the same way and its activity was compared between isolated and in situ generated complexes. In both cases a base was required to generate the free carbene, thus the base used was screened too (Table 2-2).

Table 2-2. Base scope for the generation of the free carbene



Entry	Base	In situ generated vs. Isolated copper complex	Yield (%)
1	LiHMDS	In situ generated	16
2	*n*-BuLi	In situ generated	61
3	KO*t*-Bu	In situ generated	34
4	LiHMDS	Isolated	72
5	*n*-BuLi	Isolated	61

It was encouraging to see the yield of the 1,2-addition product improved by switching from copper(I) to copper(II). Besides, the isolated NHC-Cu complexes (entries 4 and 5) gave better activities than their in situ generated analogues (entries 1-3). Although generating in situ the catalyst might be appealing (not having to isolate the metal complex), the main the drawback was the lack of control of its formation. Indeed, the base used to deprotonate the imidazolium might not completely react with the carbene precursor. Even if it did, the complexation might not be quantitative. In both cases, an excess of copper acetate could still catalyze the reaction (background reaction). However, it was challenging to handle and to monitor the isolation (hence purity) of the NHC-copper(II) complex. It was not possible to know whether the catalyst used was the desired species or mixed with an excess of copper acetate. This issue had to be kept in mind for the asymmetric reaction as free copper could hinder the enantioselectivity of the chiral ligands.

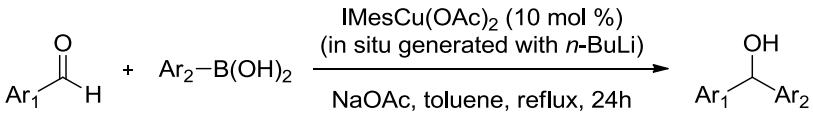
The base used for the preparation of the latter ones had an important effect in terms of activity. This was probably due to the presence of the by-product generated along with the complex. For example, both LiHMDS and KO*t*-Bu's conjugate acids are

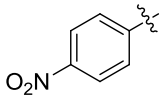
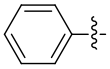
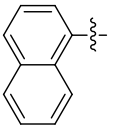
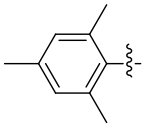
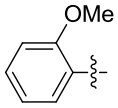
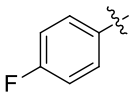
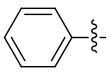
protic while *n*-BuLi gave up a simple gas as its conjugate acid. A proton source might hinder the catalytic activity of the copper complex.

Other optimizations have been performed such as reaction time (36 hours) or counter-anion of the bis(mesityl)imidazolium salt (PF_6^- and BF_4^-). None of these new conditions improved the yield of the diarylmethanol (61%, 46%, and 51%, respectively).

A substrate scope study was then undertaken with different boronic acids (Table 2-3 entries 1-4) and *p*-fluorobenzaldehyde (entry 5). Unfortunately, the conditions used were very substrate specific. For example, when more hindered boronic acids were employed, a drop of the reactivity was observed (entries 2 and 3). Also, a more electron rich boronic acid (entry 4) or another electron deficient aldehyde (entry 5) did not give better results.

Table 2-3. Substrate scope

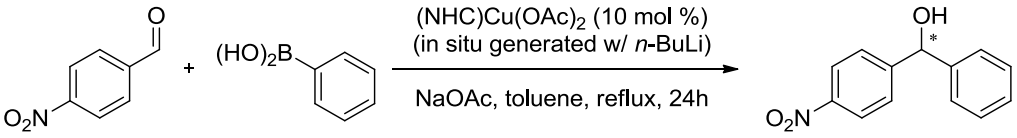


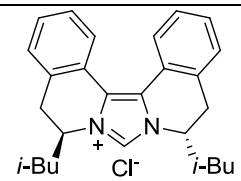
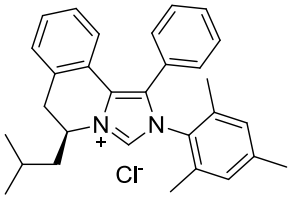
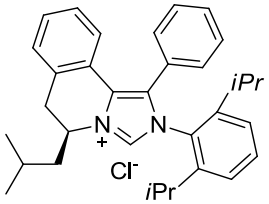
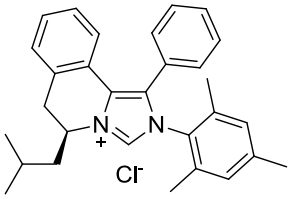
Entry	Ar_1	Ar_2	Yield (%)
1			61
2			56
3			12
4[a]			22
5			no reaction

[a] isolated IMesCuCl was used as the catalyst

Finally a chiral ligand scope could take place in order to assess their enantioselectivities (Table 2-4). It was interesting to observe that C_2-symmetric ligand offered the product in low yield and enantioselectivity in contrast with its C_1-analogue which gave better enantiomeric excess (entries 1 and 2). However, too much hindrance in the ligand was detrimental to both yield and ee (entry 3). Finally, an isolated complex gave better results as its in situ generated counterpart (entry 4). An ee of 38% was a bit lower than the one reported by Shi (45%), however, no other groups published data with the same substrates: *p*-nitrobenzaldehyde and phenylboronic acid.

Table 2-4. Chiral ligand scope



Entry	NHC precursor	Yield (%)	ee (%)
1		28	<5
2		34	27
3		38	<3
4[a]		62	38

[a] Isolated [(NHC)Cu(OAc)$_2$] complex was used instead of in situ generated

Another test reaction was the copper-catalyzed β-borylation of conjugated amide. This C_1-symmetric isoquinoline-based ligand showed good enantioselectivity in the past.[64] Unfortunately, the extra hindrance brought by the new type of ligand was not enough to increase the ee and gave similar results as its original carbene precursor (Figure 2-10).

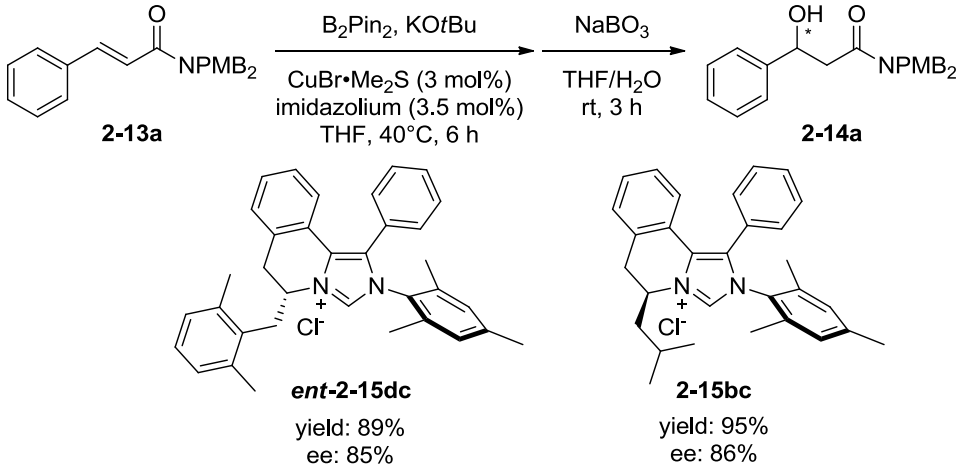


Figure 2-10. Comparison of ligands ***ent*-2-15dc** and **2-15bc** in the β-borylation of **2-13a**

Design of a Ligand Containing a Lewis Base

The improvement made on the design of the C_1-symmetric ligand could allow access to more than alkyl or aryl substituents. Indeed the aziridine opening could be carried out with nucleophiles other than organometallic reagents such as amines, or alcohols (Figure 2-11).

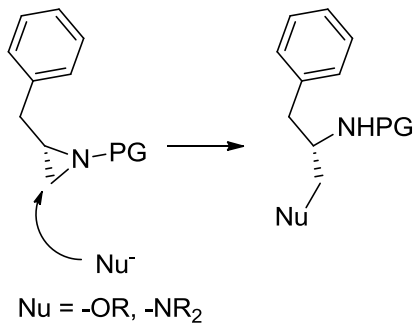
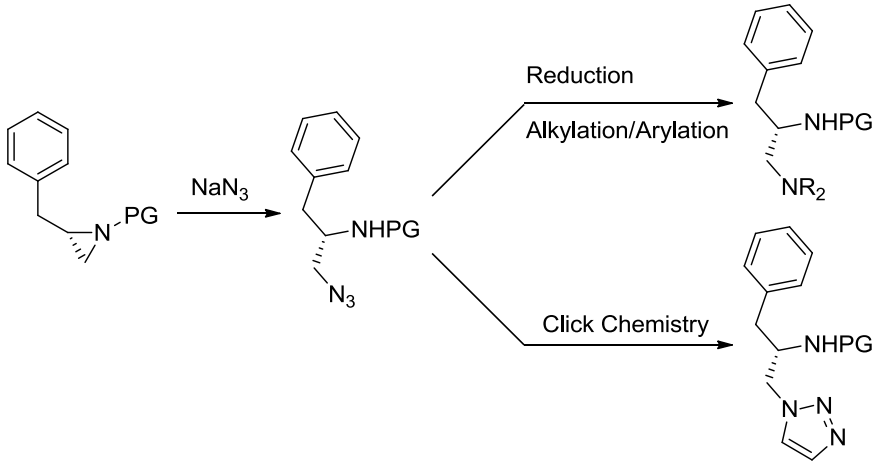


Figure 2-11. New concept for the ring opening of the aziridine moiety

The introduction of a nitrogen atom could improve the efficiency of the ligand in terms of enantioselectivity. Indeed, the new pendant could act as a potential Lewis base like an arm bringing the substrate (such as boron species) close to the metal center in a specific angle (bifunctional catalyst).

A simple way to introduce a nitrogen atom was with sodium azide (Scheme 2-8). From there, the azido group could either be reduced into the corresponding amine or after click chemistry, functionalized into a triazole moiety. The great advantage to use the latter one would be the tolerance to the different conditions to complete the ligand synthesis due to the aromaticity of the heterocycle. Therefore this pathway was explored first.

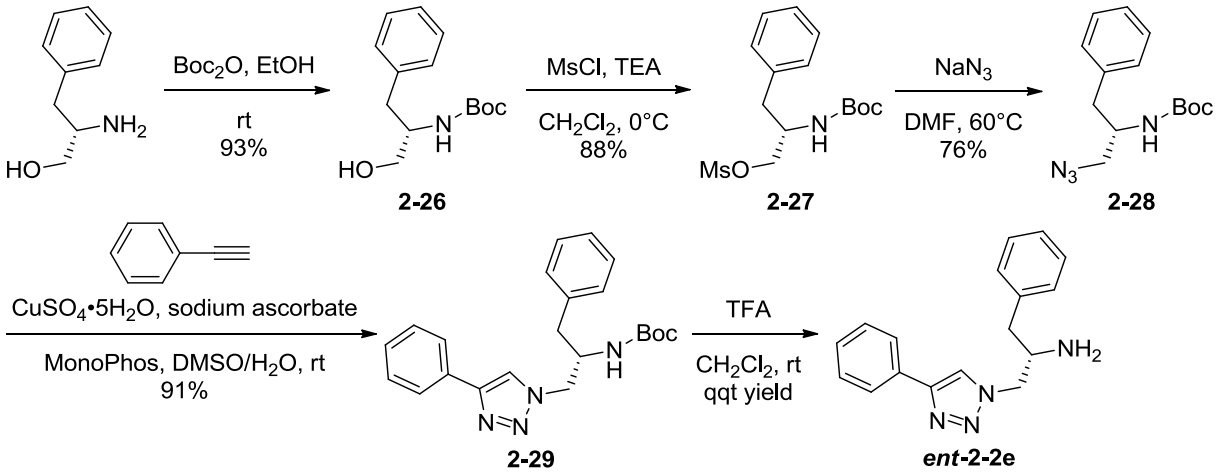


Scheme 2-8. New targets for the chiral amine containing a potential Lewis base

The previous synthesis of the free amine ***ent*-2-2d** called for a N-tosyl protection before activation of the alcohol moiety. However, its removal by lithium reduction would not be compatible with the azido pendant. Therefore another protecting group was needed which did not require reducing conditions for its cleaving. The Boc group would be a good candidate as acidic conditions would take care of its removal. Besides,

instead of forming an aziridine ring to reopen it with sodium azide, the mesylated alcohol adduct could simply be isolated and then subjected to an S_N2 reaction.

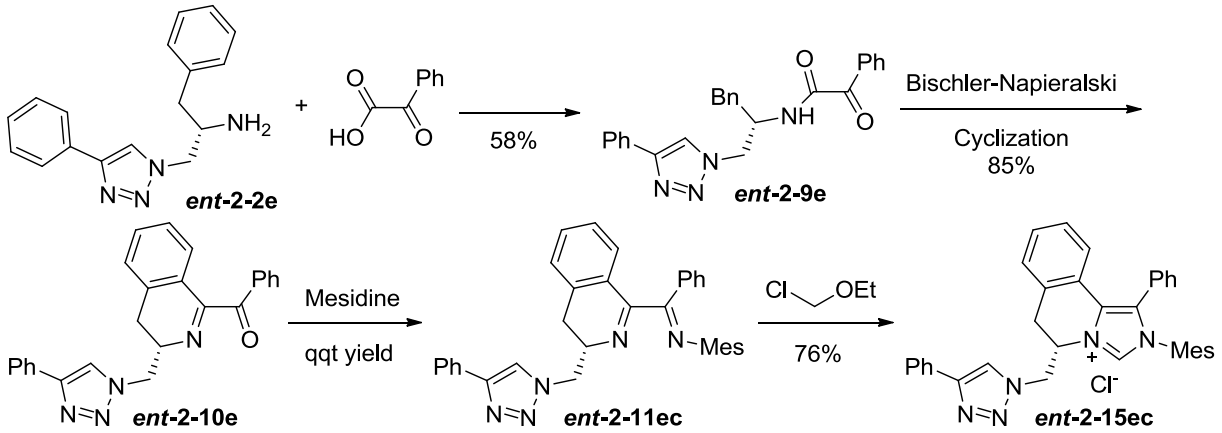
Preparation of azide **2-28** was performed according to known procedures. [81-83] The synthesis started with L-phenylalaninol that was N-Boc protected (Scheme 2-9).



Scheme 2-9. Synthesis of free amine ***ent*-2-2e**

The mesylated alcohol **2-27** was treated with sodium azide to afford the desired product **2-28**. Using Feringa's conditions for the formation of the triazole **2-29**, azide was therefore treated with phenylacetylene in the presence of copper sulfate, sodium ascorbate, and the ligand (*S*)-MonoPhos.[84] Only one regioisomer was observed as predicted. Finally, deprotection of the *tert*-butyloxycarbonyl group with trifluoroacetic acid gave free amine ***ent*-2-2e**. The C_1-symmetric ligand precursor could be synthesized using the same conditions as previously described (Scheme 2-10).

The most basic nitrogen atom of the triazole moiety was N_3 as Foces-Foces calculated the energy levels for protonated forms of 1-methyl-4-phenyl-1,2,3-triazole (Figure 2-12).[85] Therefore, the Lewis base would coordinate to an electron deficient atom (such as boron) with the N_3 nitrogen atom.



Scheme 2-10. Synthesis of imidazolium ***ent*-2-15ec**

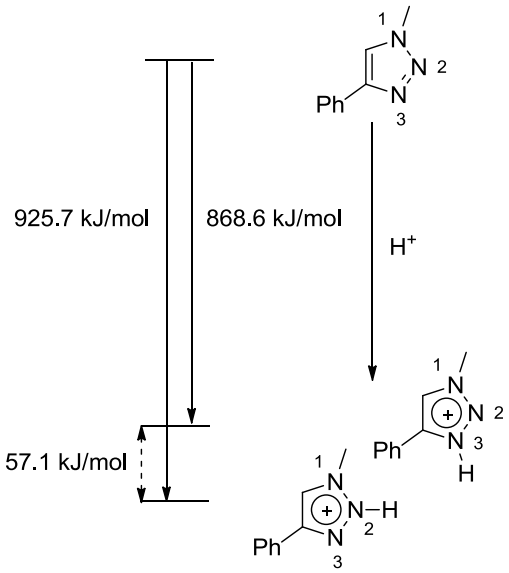


Figure 2-12. Calculated energy levels of protonated 1-methyl-4-phenyl-1,2,3-triazole

The ligand precursor was tested in the copper-catalyzed β-borylation of conjugated ester, ethyl cinnamate (Figure 2-13).[64] The efficiency of this imidazolium was then compared to the original design of the C_1-symmetric ligand. In addition to the moderate yield (65%), the enantioselectivity was also lower than the other candidate (25% vs. 55%).

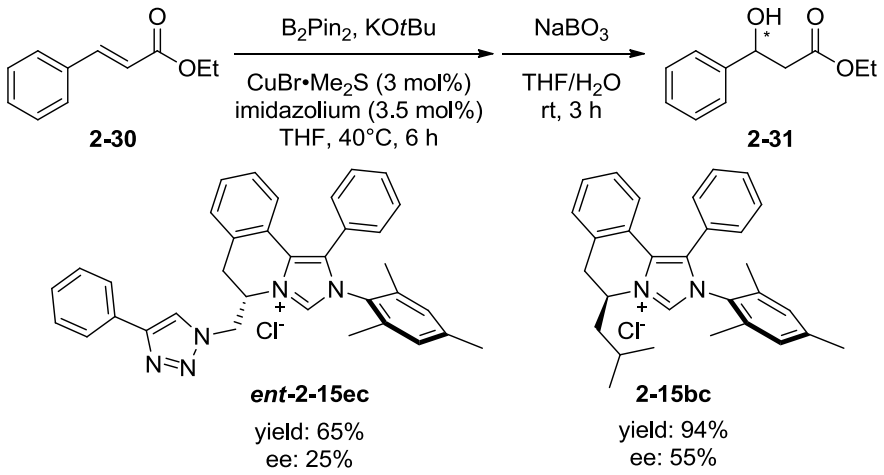


Figure 2-13. Comparison of ligands ***ent*-2-15ec** and **2-15bc** for the β-borylation of **2-30**

The lower enantioselectivity showed that the ligand is less discriminating. Maybe the arm aimed away from the metal center giving a wider angle for the substrate to approach the complex.

Since this type of ligand did not show encouraging results for the β-borylation, another reaction using boron reagents (boronic acids) was therefore tested: 1,2-addition of phenylboronic acid on substituted benzaldehyde (Figure 2-14). This addition has been previously tested with the original C_1-symmetric ligand **2-15bc**. Surprisingly, the new ligand didn't show any reactivity and the starting material was recovered.

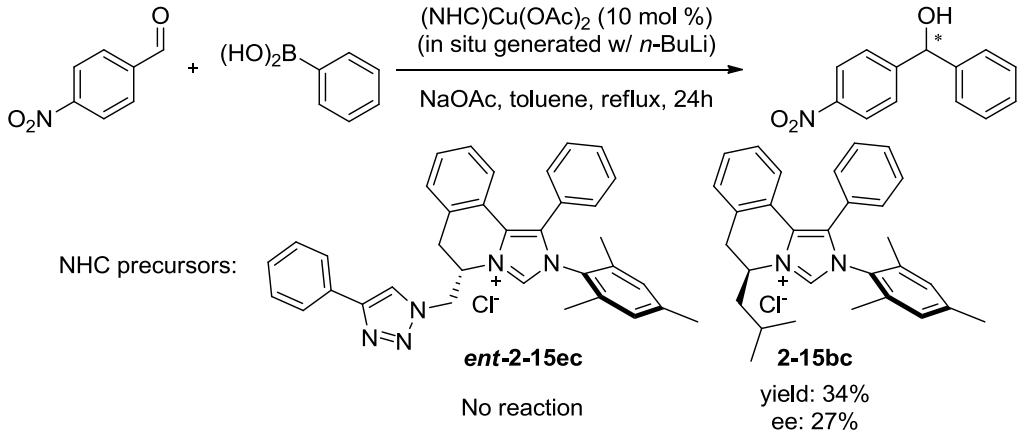


Figure 2-14. Comparison of ligands ***ent*-2-15ec** and **2-15bc** for the 1,2-addition

Maybe the triazole moiety was too strong of a Lewis base and completely inhibited the reaction by coordinating it to the phenylboronic acid. Once coordinated, the complex would be hindered and no other boronic acid or benzaldehyde derivative could approach the metal center. This could also explain why the β-borylation got also a lower yield with the same ligand.

Since the reactions using boron reagents might not be suitable for this type of ligand, a different reaction was tested: the asymmetric allylic alkylation (AAA). This time, the magnesium could coordinate to both the triazole and the substrate restraining the approach of the Grignard reagent onto the olefin. The ligand showed some enantioselectivity (26%) but not as much as a C_2-symmetric one that gave 73% ee (Figure 2-15). However, the branched/linear ratio was very high (19/1) and the reactivity was good (87% yield). The enantioselectivity might be only due to the hindrance brought by the substituted triazole. Besides, it was lower than the C_2-symmetric cyclohexyl-ligand since there is one extra methylene group bringing the bulkiness further away from the metal center.

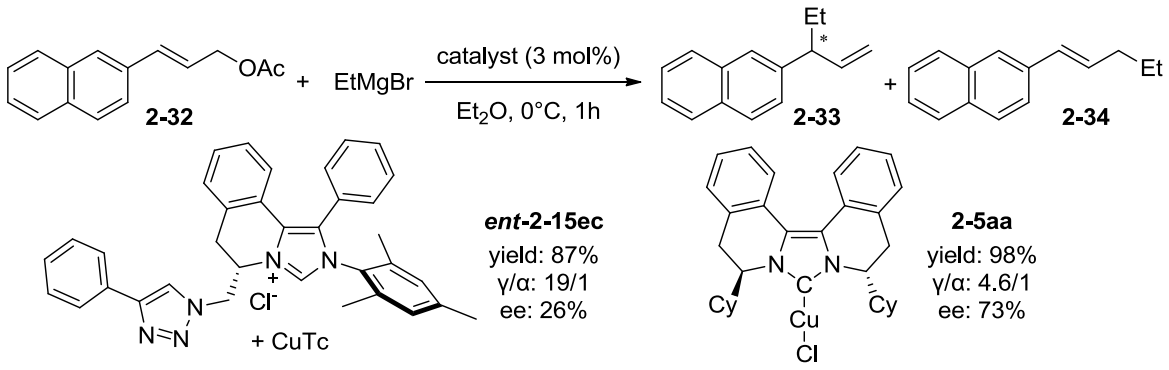


Figure 2-15. Comparison of ligands ***ent*-2-15ec** and **2-5aa** for the AAA

To see how selective the ligand precursor could be, the reaction temperature was lowered to -78°C while the other conditions remained the same. The observed ee went

up to 45% (8% yield) but it was still lower than complex **2-5aa** could offer. Besides, the regioselectivity was heavily affected (γ/α: 2.8/1).

Experimental Section

General Remarks

All the reactions were conducted in flame-dried glassware under an inert atmosphere of dry argon. THF, CH_2Cl_2, and Et_2O were passed through two packed columns of neutral alumina under positive pressure prior to use. All the chemicals used were purchased from Sigma-Aldrich Co., Acros Organics and Strem Chemicals Inc. and were used as received without further purification except for styrene, *p*-nitrobenzaldehyde and phenylboronic acid. Flash column chromatography was performed on 230-400 Mesh 60 Å Silica Gel (Whatman Inc.). NMR spectra were recorded using a FT-NMR machine, operating at 500 MHz or 300 MHz for ^{1}H NMR and at 126 MHz or 75 MHz for ^{13}C NMR. All chemical shifts for ^{1}H and ^{13}C NMR spectroscopy were referenced to residual signals from $CDCl_3$ (^{1}H) 7.26 ppm and (^{13}C) 77.23 ppm. Infrared spectra were obtained on a Perkin Elmer Spectrum RX-1 at 0.5 cm^{-1} resolution and are reported in wave numbers. High resolution mass spectra were recorded on a MALDI-TOF spectrometer, an APCI-TOF spectrometer, a DART spectrometer, or an ESI-TOF spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Enantiomer excesses were determined by chiral HPLC analysis (Shimadzu) using Chiral Technologies Chiralcel OJ-H, Chiralpak IA and IB columns and Regis Technologies Whelk-01 column.

Synthesis of Imidazolium *ent*-2-15dc

L-phenylalaninol (2-16a): To a flame-dried 500 mL three-neck round-bottom flask were added sodium borohydride (5.50 g, 145.3 mmol), THF (160 mL) and L-

phenylalanine (10.0 g, 60.5 mmol).The flask was cooled to 0°C and a solution of iodine (15.4 g, 60.5 mmol) in THF (50 mL) was added dropwise over 30 minutes. After addition of the iodine was complete and gas evolution had ceased, the flask was heated to reflux for 18 h and then cooled to room temperature, and methanol was added until the mixture became clear. After stirring 30 minutes, the solvent was removed under reduced pressure leaving a white paste which was dissolved in 20% aqueous KOH (150 mL). The solution was stirred for 4 hours and extracted with methylene chloride (x 3). The organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The crude product was recrystallized from toluene to give 7.45 g (81%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.35-7.14 (m, 5 H), 3.62 (dd, *J* = 3.8, 10.6 Hz, 1 H), 3.39 (dd, *J* = 7.1, 10.8 Hz, 1 H), 3.11 (dddd, *J* = 3.8, 5.2, 7.2, 8.7 Hz, 1 H), 2.79 (dd, *J* = 5.2, 13.4 Hz, 1 H), 2.51 (dd, *J* = 8.6, 13.4 Hz, 1 H), 2.38-0.91 (br s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 138.9, 129.4, 128.7, 126.6, 66.3, 54.4, 41.0. mp 89.7-93.2°C (lit.[86] mp 89-90°C). $[\alpha]_D^{20}$ = -21.0 (*c* 1.0, $CHCl_3$) (lit.[87] $[\alpha]_D^{20}$ = -21.7 (*c* 1.0, $CHCl_3$)).

(*S*)-2-benzyl-1-tosylaziridine (2-17a). To a flame-dried Schlenk flask, were added L-phenylalaninol (0.50 g, 3.31 mmol) and triethylamine (1.84 mL, 13.23 mmol) in methylene chloride (4.2 mL). The solution was cooled to -30°C and tosyl chloride (0.69 g, 3.64 mmol) was added portion wise. The reaction mixture was stirred for 2.5 hours at -30°C and then overnight at room temperature. The solution was cooled back to -30°C and methanesulfonyl chloride (0.27 mL, 3.51 mmol) was added dropwise. The flask was warmed to room temperature and stirred for 6 hours. The reaction was quenched with a 1 M hydrochloric acid aqueous solution. The organic layer was washed with a sodium

bicarbonate saturated aqueous solution, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate: 85/15) to give 0.49 g (63%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.69 (d, *J* = 8.2 Hz, 2 H), 7.24–7.19 (m, 2 H), 7.18–7.12 (m, 3 H), 7.09–7.00 (m, 2 H), 3.00–2.90 (m, 1 H), 2.86–2.76 (m, 1 H), 2.74–2.64 (m, 2 H), 2.43 (s, 3 H), 2.16 (d, *J* = 4.4 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 144.5, 137.2, 135.1, 129.8, 128.9, 128.6, 128.1, 126.7, 41.4, 37.7, 33.0, 21.8. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{16}H_{17}NO_2S$, 288.1053; found, 288.1045. mp 91.3–92.6°C

(*S*)-*N*-(1-(2,6-dimethylphenyl)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (2-21d). To a flame-dried Schlenk flask, was added a 1 M tetrahydrofuran solution of 2,6-dimethylphenylmagnesium bromide (2.44 mL, 2.44 mmol) in THF (4.3 mL). The solution was cooled to 0°C and copper(I) iodide (0.07 g, 0.39 mmol) was added. The reaction mixture was stirred for 30 minutes at that temperature and then cooled to -78°C. A solution of aziridine (**2-17a**) (0.35 g, 1.22 mmol) in tetrahydrofuran (2.7 mL) was added. The mixture was stirred for 15 minutes and then for 3.5 hours at 0°C. The reaction was quenched with an ammonium chloride saturated aqueous solution. The aqueous phase was extracted with diethyl ether and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate: 9/1 to 4/1) to give 0.44 g (92%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.25–7.17 (m, 5 H), 7.09–6.92 (m, 5 H), 6.88–6.82 (m, 2 H), 4.29 (d, *J* = 6.4 Hz, 1 H), 3.52 (td, *J* = 6.4, 8.5 Hz, 1 H), 2.98–2.86 (m, 2 H), 2.84–2.68 (m, 2 H), 2.36 (s, 3 H), 2.09 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 142.9, 136.9, 136.6, 134.5,

129.6, 129.4, 128.7, 128.7, 127.2, 127.2, 126.9, 126.6, 55.4, 47.0, 38.4, 21.7, 20.5. mp 118.8–120.4°C

(*S*)-1-(2,6-dimethylphenyl)-3-phenylpropan-2-amine (*ent*-2-2d). To a flame-dried Schlenk flask, was added lithium(0) (0.11 g 15.4 mmol) and naphthalene (5.6 mg, $44x10^{-3}$ mmol) in tetrahydrofuran (4.7 mL). After 30 minutes of stirring at room temperature, the solution turned deep green and was then cooled to -78°C. To the reaction mixture was added a solution of sulfonamide **2-21d** (0.43 g, 1.1 mmol) in THF (2 mL) dropwise. Next, the solution was slowly warmed to room temperature and stirred overnight. The reaction mixture was canula transferred to an Erlenmeyer flask in an ice bath. The solution was quenched with water and the aqueous layer was extracted with diethylether (x 3). To purify the free amine, the organic phase was extracted with a 1M hydrochloride solution (x 3) and after neutralization of the aqueous layer with a saturated solution of $NaHCO_3$, the phase was back extracted with ether (x 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 0.24 g (92%) of a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.35-7.16 (m, 6 H), 7.02 (s, 2 H), 3.38-3.23 (m, 1 H), 2.87-2.70 (m, 3 H), 2.63 (dd, *J* = 8.8, 13.3 Hz, 1 H), 2.33 (s, 6 H), 1.15 (br. s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 139.9, 137.2, 136.6, 129.4, 128.7, 128.6, 126.5, 126.2, 53.5, 44.8, 37.6, 20.8. HRMS (m/z): [M + H]$^+$ calcd for $C_{17}H_{21}N$, 240.1747; found, 240.1755.

(*S*)-N-(1-(2,6-dimethylphenyl)-3-phenylpropan-2-yl)-2-oxo-2-phenylacetamide (*ent*-2-9d). To a flame-dried Schlenk flask, were added benzoylformic acid (0.061 g, 0.41 mmol) and 1-hydroxybenzotriazole hydrate (0.055 g, 0.41 mmol) in methylene chloride (4 mL). The solution was stirred for 30 minutes at room temperature and amine

***ent*-2-2d** (0.098 g, 0.41 mmol), and 4-dimethylaminopyridine (5 mg, 0.04 mmol) were added to the mixture. The flask was then cooled to 0°C and a solution of *N*,*N*′-dicyclohexylcarbodiimide (0.093 g, 0.45 mmol) in methylene chloride (3 mL) was added dropwise. The reaction mixture was stirred at 0°C for 1 hour and then at room temperature overnight. The solvent was evaporated and the white solid was suspended in ethyl acetate and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (silica gel, hexanes/ethyl acetate: 85/15) to give 0.14 g (92%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.02 (d, *J* = 7.3 Hz, 2 H), 7.59-7.49 (m, 1 H), 7.43-7.15 (m, 7 H), 7.05-6.92 (m, 4 H), 4.68-4.45 (m, 1 H), 3.04-2.87 (m, 4 H), 2.32 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 188.2, 161.3, 137.9, 137.0, 134.9, 134.4, 133.3, 131.2, 129.3, 128.7, 128.6, 128.5, 126.8, 126.6, 51.3, 41.1, 34.6, 20.6. HRMS (m/z): $[M + H]^+$ calcd for $C_{25}H_{25}NO_2$, 372.1958; found, 372.1938. IR (cm^{-1}): 3328, 3021, 1656, 1596, 1535, 1449, 1233. mp 125.9-127.0°C.

(*S*)-(3-(2,6-dimethylbenzyl)-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone (*ent*-2-10d). To a flame-dried Schlenk flask, were added ketoamide ***ent*-2-9d** (0.61 g, 1.63 mmol) and 4-dimethylaminopyridine (0.60 g, 4.9 mmol) in toluene (65 mL). The solution was cooled to 0°C and triflic anhydride (1.4 mL, 8.2 mmol) was added dropwise. The reaction mixture was then heated to 90°C and stirred for 14 hours. The solution was cooled to room temperature and quenched with a sodium carbonate saturated aqueous solution. The aqueous phase was extracted with methylene chloride and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column

chromatography (silica gel, hexanes/ethyl acetate: 9/1) to give 0.50 mg (87%) of a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.04 (dd, *J* = 1.2, 7.3 Hz, 2 H), 7.62-7.54 (m, 1 H), 7.48-7.40 (m, 2 H), 7.40-7.32 (m, 2 H), 7.26-7.15 (m, 2 H), 7.09-6.99 (m, 3 H), 4.12-3.97 (m, 1 H), 3.30 (dd, *J* = 5.9, 13.8 Hz, 1 H), 3.02 (dd, *J* = 8.9, 13.9 Hz, 1 H), 2.82 (dd, *J* = 6.0, 15.8 Hz, 1 H), 2.73 (dd, *J* = 11.1, 15.8 Hz, 1 H), 2.32 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 193.6, 164.4, 137.3, 137.1, 136.1, 135.5, 134.0, 131.8, 130.7, 128.7, 128.5, 128.5, 127.4, 126.7, 126.4, 57.8, 35.1, 30.6, 20.8. HRMS (m/z): $[M + H]^+$ calcd for $C_{25}H_{23}NO$, 354.1852; found, 354.1850. IR (cm^{-1}): 3068, 3025, 2955, 2365, 2250, 1676, 1617, 1598, 1578, 1450, 1321, 1215. mp 103.7-105.8°C.

(*S*)-*N*-((3-(2,6-dimethylbenzyl)-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2,4,6-trimethylaniline (*ent*-2-11dc). To a flame-dried Schlenk flask, were added dihydroisoquinoline ***ent*-2-10d** (0.15 g, 0.42 mmol), triethylamine (0.12 mL, 0.85 mmol), and 2,4,6-trimethylaniline (0.30 mL, 2.12 mmol) in toluene (7 mL). To the solution was then added dropwise a 1M solution of titanium(IV) tetrachloride in toluene (0.51 mL, 0.51 mmol). The reaction mixture was stirred overnight at room temperature. The solution was quenched with an ammonium chloride saturated aqueous solution and the aqueous phase was extracted with methylene chloride. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate: from 99/1 to 97/3) to give 0.18 g (90%) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.07 (d, *J* = 7.9 Hz, 2 H), 7.57 - 7.38 (m, 3 H), 7.23 - 7.14 (m, 1 H), 7.14 - 6.96 (m, 5 H), 6.92 (d, *J* = 7.3 Hz, 1 H), 6.82 - 6.64 (m, 1 H), 6.57 - 6.41 (m, 1 H), 3.80 - 3.62 (m, 1 H), 3.26 (d, *J* = 11.4 Hz, 1 H), 2.79 (dd, *J* = 11.0, 13.9 Hz, 1

H), 2.42 - 1.99 (m, 15 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 146.0, 137.2, 136.4, 132.1, 131.4, 130.9, 128.9, 128.5, 128.5, 128.1, 127.9, 126.5, 126.2, 66.0, 31.8, 30.5, 22.9, 20.8, 20.7.

(*S*)-5-(2,6-dimethylbenzyl)-2-mesityl-1-phenyl-5,6-dihydro-2*H*-imidazo[5,1-*a*]isoquinolin-4-ium chloride (*ent*-2-15dc). To a flame-dried Schlenk flask, were added imine ***ent*-2-11dc** (90.0 mg, 0.167 mmol) and chloromethyl ethyl ether (106 µL, 1.15 mmol) in tetrahydrofuran (9 mL). The solution was stirred for a day at room temperature. Any volatiles were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, ethyl acetate then methylene chloride/methanol: 9/1) to give 0.10 g (quantitative yield) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.95 - 8.80 (m, 1 H), 7.49 - 7.09 (m, 10 H), 7.07 - 6.92 (m, 2 H), 6.83 (s, 1 H), 6.71 (s, 1 H), 6.15 - 6.01 (m, 1 H), 4.01 (dd, *J* = 6.0, 16.0 Hz, 1 H), 3.25 - 3.10 (m, 2 H), 2.98 (dd, *J* = 5.3, 14.7 Hz, 1 H), 2.20 (s, 9 H), 1.92 (s, 3 H), 1.86 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 141.1, 137.6, 136.4, 134.2, 132.7, 132.4, 130.9, 130.6, 130.5, 130.1, 129.9, 129.5, 129.3, 127.9, 127.5, 126.4, 125.7, 124.7, 54.0, 34.0, 32.9, 22.9, 20.4, 17.9.

Synthesis of Imidazolium *ent*-2-15ec

(*S*)-*tert*-butyl (1-hydroxy-3-phenylpropan-2-yl)carbamate (2-26). To a round bottom flask, were added L-phenylalaninol (4 g, 26.45 mmol) in ethanol (52 mL) and di-*tert*-butyl dicarbonate (6.06 g, 27.77 mmol). The reaction was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure. The crude material was recrystallized in hexanes to afford 6.18 g (93%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.41–7.07 (m, 5 H), 4.71 (br. s., 1 H), 4.00–3.79 (m, 1 H),

3.75–3.62 (m, 1 H), 3.60–3.49 (m, 1 H), 2.84 (d, *J* = 7.0 Hz, 1 H), 2.25 (br. s., 1 H), 1.42 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 156.4, 138.0, 129.6, 128.7, 126.6, 79.9, 64.3, 53.9, 37.6, 28.5. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{14}H_{21}NO_3$, 274.1414; found, 274.1423.

(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropyl methanesulfonate (2-27). To a flame-dried Schlenk flask was added alcohol **2-26** (4.0 g, 15.92 mmol) in methylene chloride (50 mL). The solution was then cooled to 0°C and to the mixture were added triethylamine (2.44 mL, 17.51 mmol) and methanesulfonyl chloride (1.30 mL 16.71 mmol) in methylene chloride (30 mL) dropwise. The solution was stirred for 1 hour at 0°C then overnight at room temperature. Next, 30 mL of water were added and the aqueous phase was extracted 3 times with methylene chloride. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate: 1/1) to give 4.57 g (88%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.42–7.12 (m, 5 H), 4.72 (br. s., 1 H), 4.32–4.19 (m, 1 H), 4.16–4.02 (m, 2 H), 3.02 (s, 3 H), 2.94–2.78 (m, 2 H), 1.42 (s, 9 H) ^{13}C NMR (75 MHz, $CDCl_3$, δ): 155.3, 136.8, 129.4, 129.0, 127.2, 80.2, 70.0, 51.0, 37.5, 37.4, 28.5. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{15}H_{23}NO_5S$, 352.1189; found, 352.1195. IR (cm^{-1}): 3363, 2980, 1751, 1682, 1524, 1458, 1355, 1281, 1167, 1058, 984, 971, 841, 752, 703.

(*S*)-*tert*-butyl (1-azido-3-phenylpropan-2-yl)carbamate (2-28). To a flame-dried Schlenk flask, were added **2-27** (4.00 g, 12.14 mmol) and sodium azide (0.97 g, 15.0 mmol) in DMF (15 mL). The reaction mixture was heated to 60°C and stirred at that temperature overnight. After the solution cooled to room temperature, water was added

and the aqueous phase was extracted six times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, hexanes/ethyl acetate: 1/1) to afford 2.54 g (76%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.39–7.10 (m, 5 H), 4.64 (br. s., 1 H), 4.07–3.87 (m, 1 H), 3.42 (dd, *J* = 4.4, 12.3 Hz, 1 H), 3.31 (dd, *J* = 4.4, 12.3 Hz, 1 H), 2.88 (dd, *J* = 6.4, 13.2 Hz, 1 H), 2.78 (dd, *J* = 7.9, 13.5 Hz, 1 H), 1.43 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 155.3, 137.3, 129.5, 128.9, 127.0, 80.0, 53.3, 51.6, 38.4, 28.6. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{14}H_{20}N_4O_2$, 299.1478; found, 299.1489. IR (cm^{-1}): 3338, 2977, 2374, 2102, 1686, 1509, 1459, 1364, 1251, 1168, 1053, 1026, 742, 701. $[\alpha]_D^{20}$ -11.9 (*c* 1.01, $CHCl_3$).

(*S*)-*tert*-butyl (1-phenyl-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propan-2-yl)carbamate (2-29). To a sample vial were added copper(II)sulfate pentahydrate (11.2 mg, 44.9 x 10^{-3} mmol) and sodium ascorbate (44.4 mg, 0.22 mmol) in distilled water (9.6 mL). To the sample vial was added (*S*)-MonoPhos (18.0 mg, 50.0 x 10^{-3} mmol) in dimethylsulfoxide (3.2 mL). The resulting solution was vigorously stirred for 15 minutes. The solution was then added to a round bottom flask containing a solution of azide **2-28** (1.24 g, 4.49 mmol) and phenylacetylene (1.0 mL, 8.98 mmol) in a DMSO/H_2O mixture (24 mL DMSO/H_2O: 1/3). The reaction mixture was vigorously stirred at room temperature for 20 hours and diluted with 60 mL of water. The aqueous phase was extracted with methylene chloride and the combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was recrystallized in ethanol with some drops of water to give 1.55 g (91%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.83 (d, *J* = 7.0 Hz, 2 H), 7.74 (s, 1 H), 7.49–7.40

(m, 2 H), 7.39–7.31 (m, 3 H), 7.30–7.22 (m, 3 H), 4.83 (br. s., 1 H), 4.54 (d, *J* = 5.0 Hz, 2 H), 4.36–4.21 (m, 1 H), 3.01–2.76 (m, 2 H), 1.39 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 155.5, 147.8, 136.9, 130.7, 129.5, 129.1, 129.0, 128.4, 127.2, 125.9, 121.0, 80.2, 69.9, 52.2, 38.2, 28.5. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{22}H_{26}N_4O_2$, 401.1948; found, 401.1959. IR (cm^{-1}): 3370, 2978, 2375, 1686, 1509, 1250, 1170, 1057, 764, 697. $[\alpha]_D^{20}$ -0.9 (*c* 1, $CHCl_3$)

(*S*)-1-phenyl-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propan-2-amine (*ent*-2-2e). To a flame-dried Schlenk flask, was added triazole **2-26** (1.02 g, 2.69 mmol) in a 1:1 mixture of methylene chloride and trifluoroacetic acid (26 mL). The reaction mixture was stirred for 2 hours at room temperature and the volatiles were evaporated under reduced pressure. To the crude product was added a 1M aqueous sodium hydroxide solution in methylene chloride and stirred for 15 minutes. The aqueous phase was extracted with methylene chloride and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The beige solid didn't need any further purification (0.75 g, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.92–7.78 (m, 3 H), 7.49–7.39 (m, 2 H), 7.38–7.30 (m, 3 H), 7.30–7.20 (m, 3 H), 4.49 (dd, *J* = 4.1, 13.5 Hz, 1 H), 4.26 (dd, *J* = 7.9, 13.8 Hz, 1 H), 3.63 (ddt, *J* = 4.1, 5.4, 8.2 Hz, 1 H), 2.89 (dd, *J* = 5.3, 13.5 Hz, 1 H), 2.64 (dd, *J* = 8.2, 13.5 Hz, 1 H), 1.32 (br. s., 2 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 137.7, 130.8, 129.5, 129.1, 129.0, 128.4, 127.1, 125.9, 120.9, 100.0, 56.7, 53.1, 41.8. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{17}H_{18}N_4$, 301.1424; found, 301.1432. IR (cm^{-1}): 3358, 3304, 3091, 3034, 2926, 2346, 1750, 1610, 1467, 1442, 1226, 1084, 1054, 975, 830, 767,749, 697. $[\alpha]_D^{20}$ -12.3 (*c* 1.0, $CHCl_3$).

(*S*)-2-oxo-2-phenyl-*N*-(1-phenyl-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propan-2-yl)acetamide (*ent*-2-9e). To a flame-dried Schlenk flask, were added benzoylformic acid (0.17 g, 1.11 mmol) and 1-hydroxybenzotriazole hydrate (0.15 g, 1.11 mmol) in methylene chloride (7 mL). The solution was stirred for 30 minutes at room temperature and amine ***ent*-2-2e** (0.31 g, 1.11 mmol), and 4-dimethylaminopyridine (14 mg, 0.11 mmol) were added to the mixture. The flask was then cooled to 0°C and a solution of *N*,*N*′-dicyclohexylcarbodiimide (0.25 g, 1.22 mmol) in methylene chloride (5 mL) was added dropwise. The reaction mixture was stirred at 0°C for 1 hour and then at room temperature overnight. The solvent was evaporated and the white solid was suspended in ethyl acetate and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (silica gel, hexanes/ethyl acetate: 3/2) to give 0.12 g (58%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.17 (dd, *J* = 1.3, 8.4 Hz, 2 H), 7.84–7.77 (m, 4 H), 7.60 (tt, *J* = 1.3, 7.4 Hz, 1 H), 7.46–7.40 (m, 5 H), 7.38–7.32 (m, 2 H), 7.31–7.27 (m, 2 H), 5.24 (br. s, 1 H), 4.79–4.69 (m, 1 H), 4.65 (dd, *J* = 4.9, 14.1 Hz, 1 H), 4.58 (dd, *J* = 6.2, 14.1 Hz, 1 H), 3.01 (dd, *J* = 7.1, 14.0 Hz, 1 H), 2.96 (dd, *J* = 7.3, 14.1 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 187.3, 162.1, 148.2, 136.1, 134.8, 133.1, 131.3, 130.5, 129.5, 129.2, 129.1, 128.8, 128.5, 127.6, 126.0, 120.9, 51.1, 49.4, 37.8. HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{25}H_{22}N_4O_2$, 433.1635; found, 433.1642.

(*S*)-phenyl(3-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-3,4-dihydroisoquinolin-1-yl)methanone (*ent*-2-10e). To a flame-dried Schlenk flask, were added ketoamide ***ent*-2-9e** (84 mg, 0.204 mmol) and 4-dimethylaminopyridine (75 mg, 0.613 mmol) in toluene (8 mL). The solution was cooled to 0°C and triflic anhydride (0.34 mL, 2.04 mmol) was

added dropwise. The reaction mixture was then heated to 90°C and stirred for 14 hours. The solution was cooled to room temperature and quenched with a sodium carbonate saturated aqueous solution. The aqueous phase was extracted with methylene chloride and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate: 1/1) to give 68.4 mg (85%) of a beige solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.95 - 7.82 (m, 3 H), 7.81 - 7.69 (m, 2 H), 7.59 - 7.49 (m, 2 H), 7.46 - 7.29 (m, 10 H), 4.93 (dd, *J* = 4.8, 13.7 Hz, 1 H), 4.83 (d, *J* = 5.6, 13.7 Hz, 1 H), 4.25 - 4.06 (m, 1 H), 2.95 (dd, *J* = 5.6, 16.4 Hz, 1 H), 2.81 - 2.63 (m, 1 H).

(*S*,*E*)-2,4,6-trimethyl-*N*-(phenyl(3-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-3,4-dihydroisoquinolin-1-yl)methylene)aniline (*ent*-2-11ec). To a flame-dried Schlenk flask, were added dihydroisoquinoline ***ent*-2-10e** (68 mg, 0.174 mmol), triethylamine (49 µL, 0.349 mmol), and 2,4,6-trimethylaniline (122 µL, 0.871 mmol) in toluene (3 mL). To the solution was then added dropwise a 1M solution of titanium(IV) tetrachloride in toluene (209 µL, 0.209 mmol). The reaction mixture was stirred overnight at room temperature. The solution was quenched with an ammonium chloride saturated aqueous solution and the aqueous phase was extracted with methylene chloride. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate: from 1/0 to 3/1) to give 88.8 mg (quantitative yield) of a yellow solid.

(*S*)-2-mesityl-1-phenyl-5-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-5,6-dihydro-2*H*-imidazo[5,1-*a*]isoquinolin-4-ium chloride (*ent*-2-15ec). To a flame-dried Schlenk

flask, were added imine ***ent*-2-11ec** (84.6 mg, 0.167 mmol) and chloromethyl ethyl ether (92 μL, 0.996 mmol) in tetrahydrofuran (8 mL). The solution was stirred for a day at room temperature. Any volatiles were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, ethyl acetate then methylene chloride/methanol: 9/1) to give 70.8 mg (76%) of a beige solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 9.66 (s, 1 H), 8.88 (s, 1 H), 7.85 (d, *J* = 7.3 Hz, 2 H), 7.48–7.42 (m, 2 H), 7.40–7.33 (m, 4 H), 7.30 (d, *J* = 7.1 Hz, 2 H), 7.23 (d, *J* = 7.4 Hz, 2 H), 7.15–7.08 (m, 2 H), 6.90 (s, 1 H), 6.72 (s, 1 H), 6.38 (br. s., 1 H), 4.93 (dd, *J* = 7.3, 13.7 Hz, 1 H), 4.88 (dd, *J* = 5.1, 13.7 Hz, 1 H), 3.76 (dd, *J* = 4.3, 16.7 Hz, 1 H), 3.33 (d, *J* = 16.6 Hz, 1 H), 2.22 (s, 3 H), 2.13 (s, 3 H), 1.82 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 148.7, 141.3, 136.5, 135.2, 134.8, 131.1, 131.0, 130.5, 130.4, 130.1, 130.0, 129.9, 129.8, 129.8, 129.5, 128.9, 128.9, 128.3, 128.2, 126.4, 126.1, 125.2, 125.0, 122.5, 122.4, 54.2, 51.3, 30.8, 21.2, 18.1, 18.0. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{35}H_{32}N_5$, 522.2652; found, 522.2664. IR (cm^{-1}): 3422, 2957, 2237, 1610, 1542, 1476, 1438, 1364, 1341, 1217, 1078, 1042, 912, 856, 769, 731, 697.

β-Borylation Reaction of Conjugated Ester 2-30 or Conjugated Amide 2-13a

Typical procedure

To a flame-dried Schlenk flask was added copper(I) bromide-dimethylsulfide complex (3 mol%), NHC ligand precursor (3.5 mol%), potassium *tert*-butoxide (9 mol%) and THF (0.16 M). The reaction mixture was stirred for 30 minutes at room temperature. Then bis(pinacolato)diboron (0.178 mmol) was added followed by amide (0.162 mmol) and methanol (0.324 mmol). Then the reaction mixture was stirred at 40°C for 6 h. $NaBO_3•(H_2O)_4$ (0.810 mmol) and water (0.16 M) were added and the reaction mixture

was stirred an additional 3 h at room temperature. The suspension was then extracted with Et_2O (3 x 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Silicagel column chromatography with a mixture of hexane and ethyl acetate as the eluent gave the chiral β alcohol. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.45-7.23 (m, 5 H), 7.14 (d, *J* = 8.5 Hz, 2 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 6.95-6.79 (m, 4 H), 5.22 (br. s., 1 H), 4.87 (d, *J* = 2.9 Hz, 1 H), 4.61 (d, J = 14.7 Hz, 1 H), 4.45 (d, *J* = 14.4 Hz, 1 H), 4.30 (d, *J* = 4.1 Hz, 2 H), 3.81 (s, 3 H), 3.81 - 3.79 (m, 3 H), 2.87 - 2.75 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 172.6, 159.1, 159.0, 142.9, 129.6, 128.8, 128.4, 127.6, 127.4, 125.7, 114.3, 114.0, 70.6, 55.3, 49.0, 47.2, 41.6. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{25}H_{27}NO_4$, 406.2013; found, 406.2011.

HPLC spectra for amide 2-14a

The enantiomeric excess was measured by chiral HPLC with a Whelk-01 column (UV 215 nm, 30% isopropanol/hexane, 1.5 mL/min).

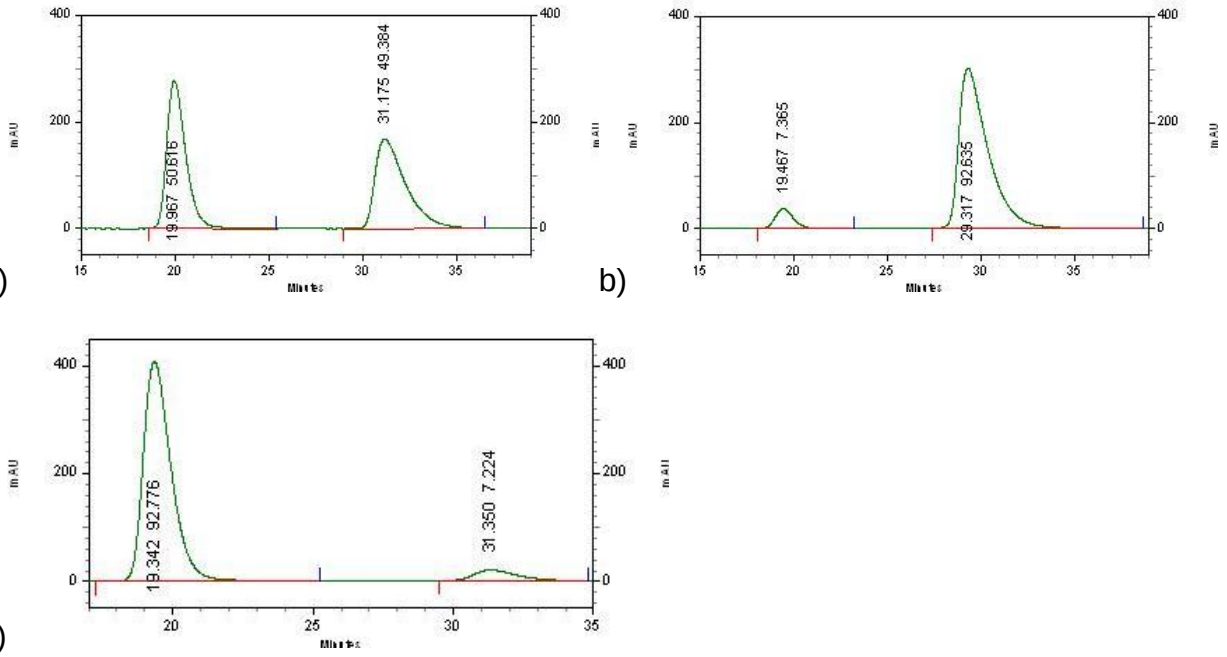


Figure 2-16. HPLC spectra for the β-borylation of amide **2-14a** a) racemic mixture, b) with ***ent*-2-15dc**, and c) with **2-15bc**

HPLC spectra for ester 2-31

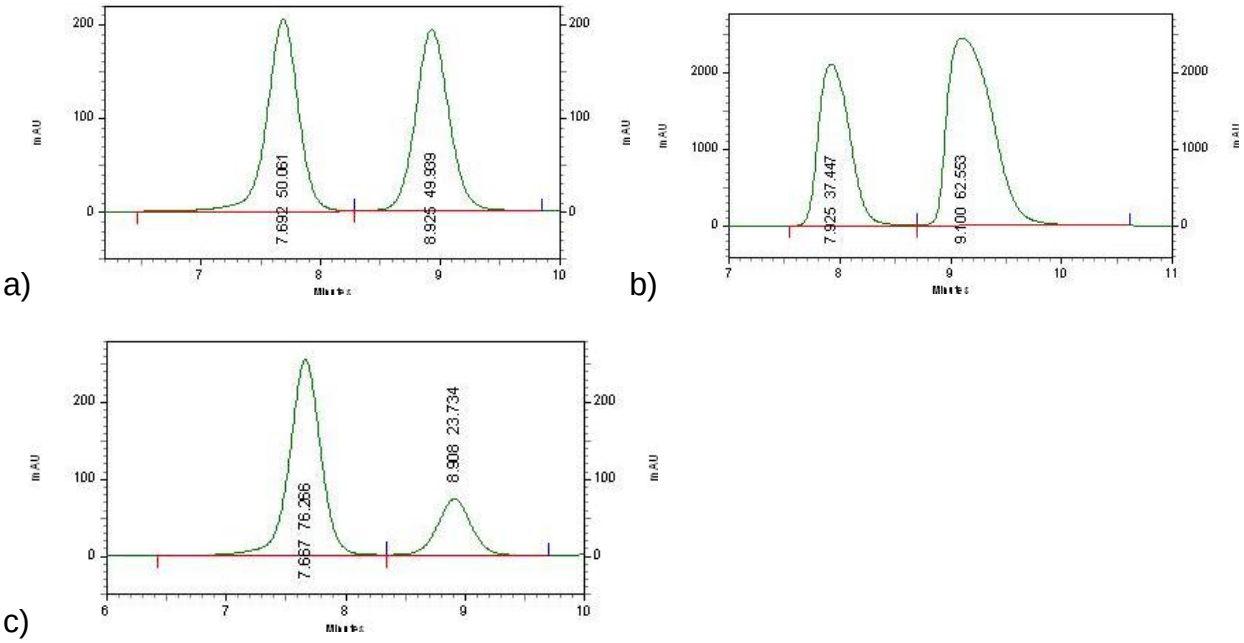


Figure 2-17. HPLC spectra for the β-borylation of ester **2-31a** a) racemic mixture, b) with ***ent*-2-15ec**, and c) with **2-15bc**

1,2-Addition Reaction

Typical procedure

In a flame dried Schlenk flask, were added IMes·HCl (8.2 mg, 0.024 mmol), copper(II) diacetate (3.6 mg, 0.02 mmol) and toluene (3 mL). The mixture was cooled to -78°C and a solution of *n*-BuLi (15 µL, 1.6M in hexane) was slowly added. After 30 minutes of stirring at room temperature, *p*-nitrobenzaldehyde (30 mg, 0.2 mmol), phenylboronic acid (48.8 mg, 0.4 mmol), and sodium acetate (49.2 mg, 0.6 mmol) were added (in the case of an isolated copper complex, the latter and toluene were added with the other reagents). The solution was stirred for 24 hours at reflux temperature. Then the flask was cooled to room temperature and water was added to the black mixture. The aqueous phase was extracted with methylene chloride (x 3) and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated

under reduce pressure. The crude material was purified by column chromatography (Silica gel, hexanes/ethyl acetate: 90/10) to afford the desired product (27.5 mg, 60%) as a white solid.

Characterization of 1,2-addition products (Table 2-3)

(4-nitrophenyl)(phenyl)methanol. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.16 (d, *J* = 8.8 Hz, 2 H), 7.56 (d, *J* = 8.2 Hz, 2 H), 7.41 - 7.29 (m, 5 H), 5.89 (s, 1 H), 2.60 (br. s., 1 H).

Naphthalen-1-yl(4-nitrophenyl)methanol. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.16 (d, *J* = 8.8 Hz, 2 H), 8.07 - 7.96 (m, 1 H), 7.93 - 7.79 (m, 2 H), 7.59 (dd, *J* = 0.8, 9.1 Hz, 2 H), 7.53 - 7.43 (m, 4 H), 6.56 (s, 1 H), 2.65 (br. s, 1 H).

Mesityl(4-nitrophenyl)methanol. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.15 (d, *J* = 9.1 Hz, 2 H), 7.47 (dd, *J* = 1.1, 9.1 Hz, 2 H), 6.88 (s, 2 H), 6.39 - 6.32 (s, 1 H), 2.29 (s, 3 H), 2.28 (br. s., 1 H), 2.22 (s, 6 H).

(4-methoxyphenyl)(4-nitrophenyl)methanol. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.41 - 7.36 (m, 2 H), 7.36 - 7.30 (m, 2 H), 7.30 - 7.19 (m, 3 H), 7.06 - 6.91 (m, 1 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 6.06 (s, 1 H), 3.81 (s, 3 H), 3.09 – 3.03 (br. s., 1 H).

HPLC spectra for the ligand scope (Table 2-4)

The enantiomeric excess was determined by HPLC analysis with a chiral column (Chiralcel IA; hexanes/2-propanol, 9:1; flow rate 1mL/min; t_R11.7 and 13.6 min).

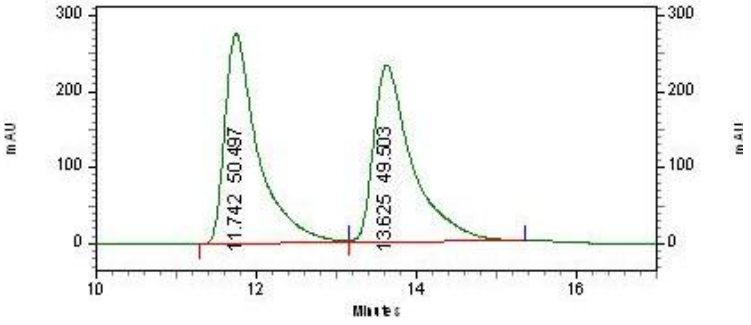


Figure 2-18. HPLC spectra of the 1,2-addition product (racemic mixture)

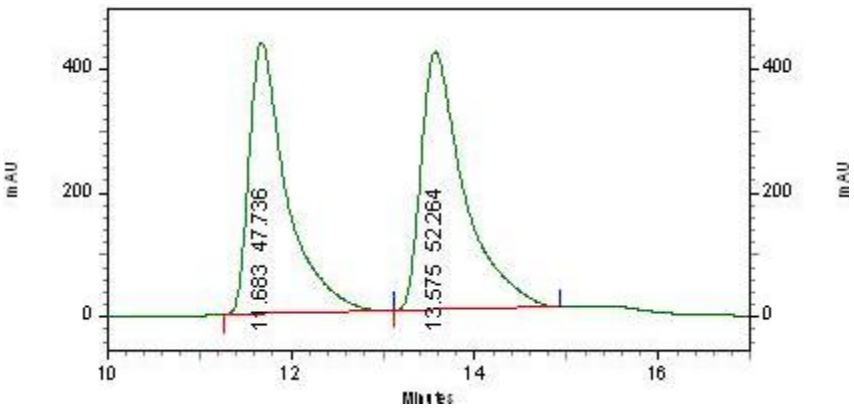


Figure 2-19. HPLC spectra of the 1,2-addition product (Table 1, entry 1)

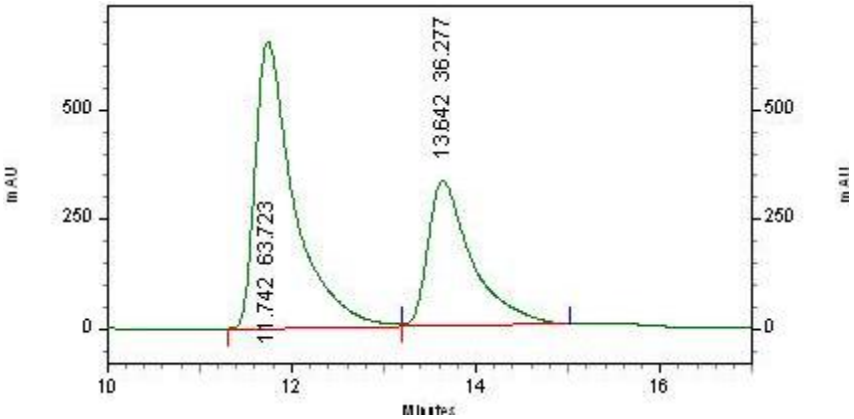


Figure 2-20. HPLC spectra of the 1,2-addition product (Table 1, entry 2)

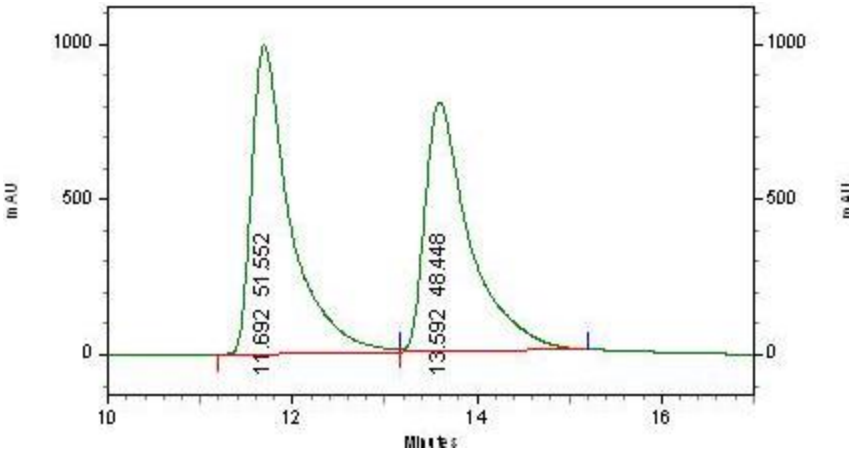


Figure 2-20. HPLC spectra of the 1,2-addition product (Table 1, entry 3)

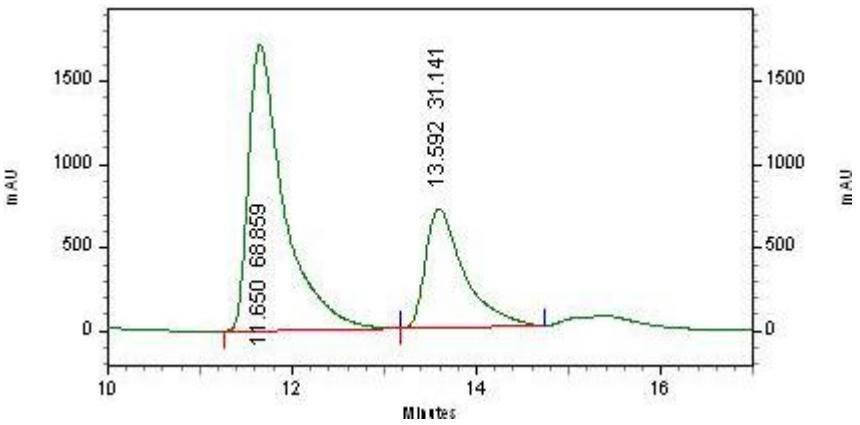


Figure 2-21. HPLC spectra of the 1,2-addition product (Table 1, entry 4)

Asymmetric Allylic Alkylation

Typical procedure

To a flame-dried Schlenk flask were added CuTC (3 mol%), chloroamidinium salt ***ent*-2-15ec** (3 mol%) and 1 mL of diethyl ether. To this solution was added an ethylmagnesium chloride solution (0.27 mmol, 2M in Et_2O) at 0°C. The mixture reaction was stirred for 5 min at 0°C. In the case of catalyst **2-5aa**, the complex was added just before the Grignard reagent. Then a solution of substrate **2-32** (0.18 mmol) in 1 mL of Et_2O was added over a 15 min period. After 1 hour, the reaction was quenched by a saturated aqueous NH_4Cl solution and extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the alkylated products **2-33** and **2-34**.

NMR spectra for the regioselectivity

The regioselectivity (S_N2': S_N2) was determined by ^1H NMR. The integration values of the olefinic proton signal of the two regioisomers were compared.

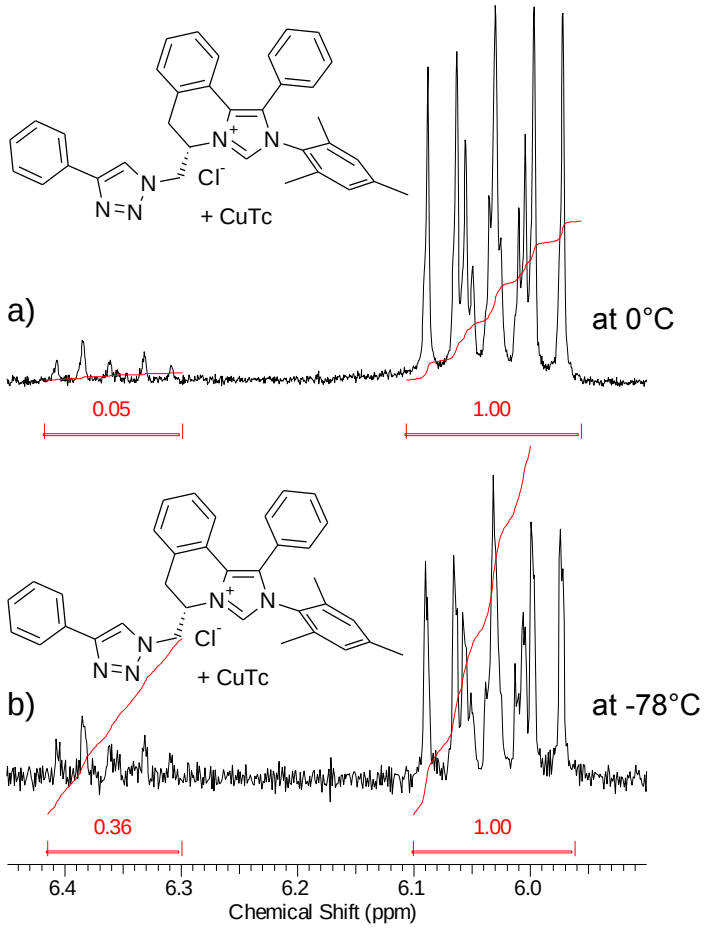


Figure 2-22. NMR spectra of the product of the AAA with ***ent*-2-15ec** a) at 0°C and b) at -78°C

HPLC spectra for the ligand scope

Enatiomeric excess was measured by chiral HPLC with a Whelk-O1 column (UV 254 nm, 100% pentane, 0.2 mL/min). t_S: 25.5 min, t_R : 26.9 min.

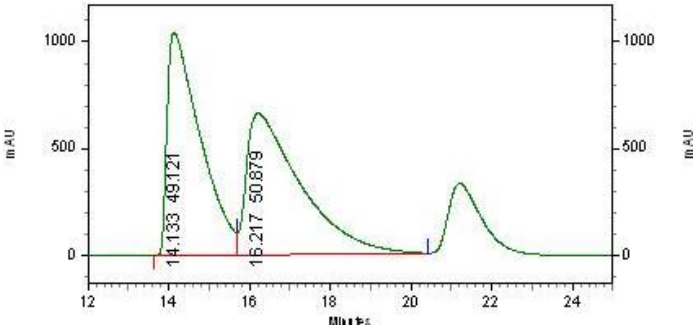


Figure 2-23. HPLC spectra of product **2-33** (racemic mixture)

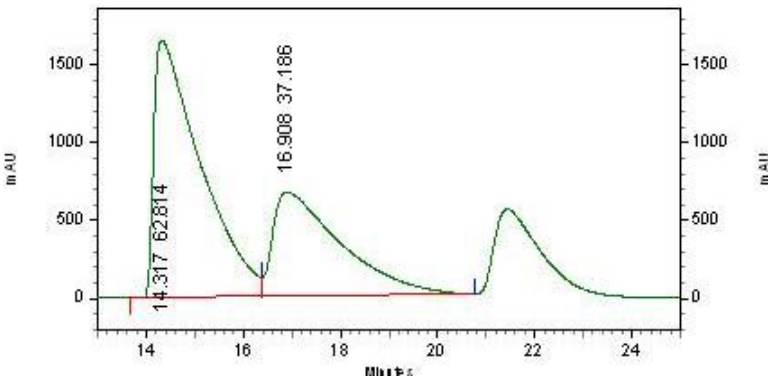


Figure 2-24. HPLC spectra of product **2-33** with ***ent*-2-15ec**

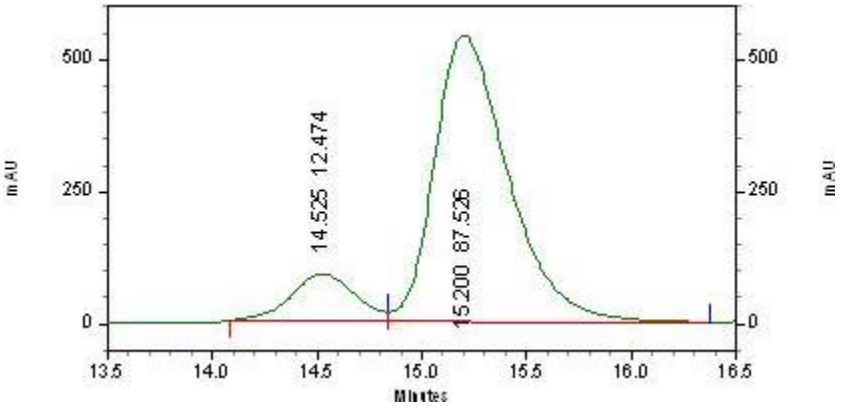


Figure 2-25. HPLC spectra of product **2-33** with with ***ent*-2-5aa**

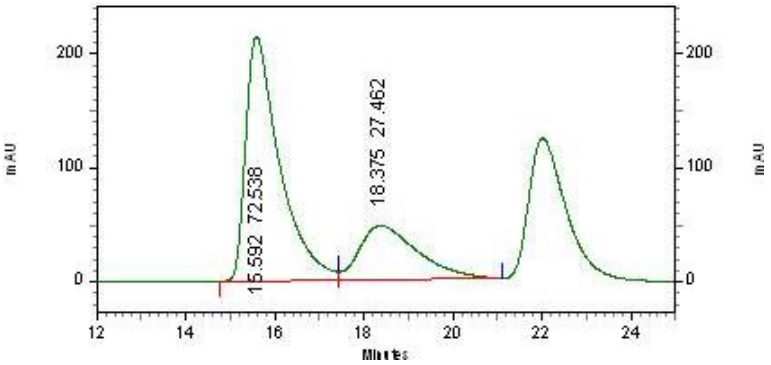


Figure 2-26. HPLC spectra of product **2-33** with ***ent*-2-15ec** at -78°C

CHAPTER 3
DESIGN, SYNTHESIS, AND APPLICATIONS OF CHIRAL AND ACHIRAL ACYCLIC DIAMINOCARBENE-METAL COMPLEXES

Achiral Acyclic Diaminocarbene Metal Complexes

ADC-Copper Catalyzed Allylic Alkylation[88]

Although acyclic diaminocarbene (ADC) ligands haven't been as much explored as their cyclic analogues, they had the advantage to be better σ-donors and more sterically demanding due to a wider N-C-N angle.[42, 48] However, the free ligands were less stable than the NHC ones making their preparation more challenging.

It had been observed that asymmetric allylic alkylation (AAA) of protected diol **3-1a** could be catalyzed by a mixture of a chloroimidazolium and a copper(I) source (Figure 3-1). Although it gave lower yield than its isolated complex, it still afforded a similar branched:linear product ratio and above all, it gave the same enantioselectivity.

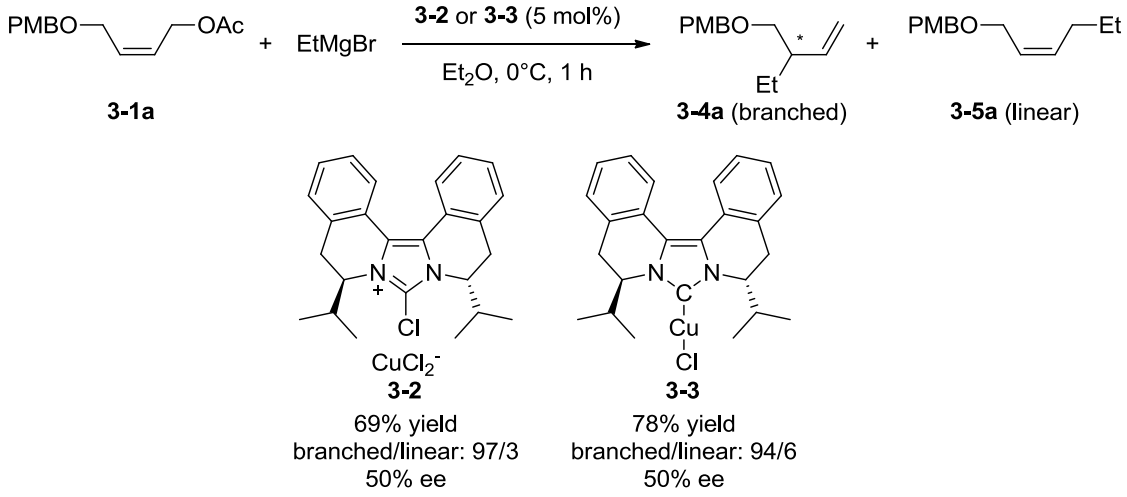
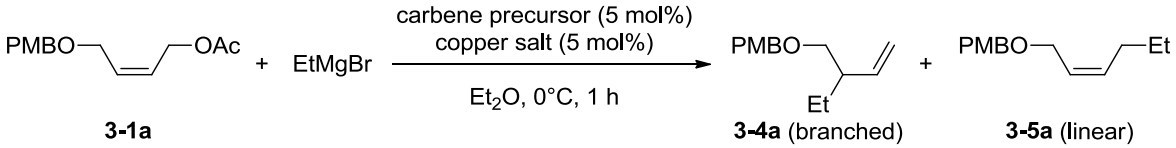


Figure 3-1. Catalytic activity of **3-2** in asymmetric allylic alkylation

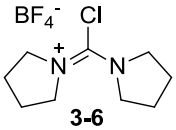
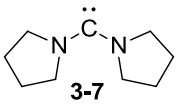
This example showed the generation of a carbene-copper complex having similar behavior as its isolated counterpart. This new in situ generation might be interesting to explore with the acyclic version, known to be more challenging to isolate. Indeed,

substituting chloroimidazolium **3-2** by commercially available chloroamidinium **3-6** gave better reactivity in the same conditions (Table 3-1, entry 1). This promising result led to optimizing the reaction conditions starting with the copper source. The oxidation state of copper didn't seem to interfere in the activity of the catalyst as similar results with either CuCl or CuTC were observed (entries 1-3). CuTC (copper thiophene-2-carboxylate) being easier to handle than CuCl (air and moisture more stable and molecular weight nearly twice more important) was chosen as the copper source for further scopes.

Table 3-1. Optimization of conditions for the copper catalyzed allylic alkylation



3-1a **3-4a** (branched) **3-5a** (linear)

Entry	Carbene precursor	Copper salt	Yield (%)	Branched : linear
1	 **3-6**	$CuCl_2$	82	93 : 7
2		CuCl	81	93 : 7
3		CuTC	83	94 : 6
4	 **3-7**	CuTC	71	90 : 10
5	**IMes**	CuTC	57	92 : 8
6	**3-6**	–	25	94 : 6
7	–	CuTC	9	13 : 87

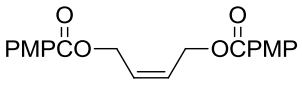
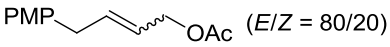
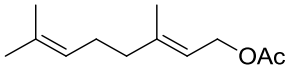
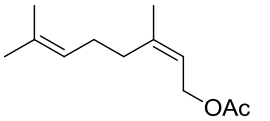
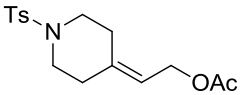
Then, it was interesting to investigate the carbene source. For example, when corresponding prepared free carbene was used in the presence of CuTC, the results were similar (entry 4). However, if a more sterically demanding cyclic free carbene (IMes) was used, then the reactivity dropped but still with the same branched/linear ratio (entry 5).

Finally, the background reaction was also studied. While the absence of copper source gave lower reactivity, the magnesium could still catalyze the reaction giving

same ratio in the products (entry 6).[89] However, if the carbene source was removed then linear product **3-5a** was the major one but in low yield (entry 7).[90]

Other substrates have also been tested in the allylic alkylation giving good branched/linear ratios (Table 3-2).

Table 3-2. Substrate scope for ADC-copper catalyzed allylic alkylation

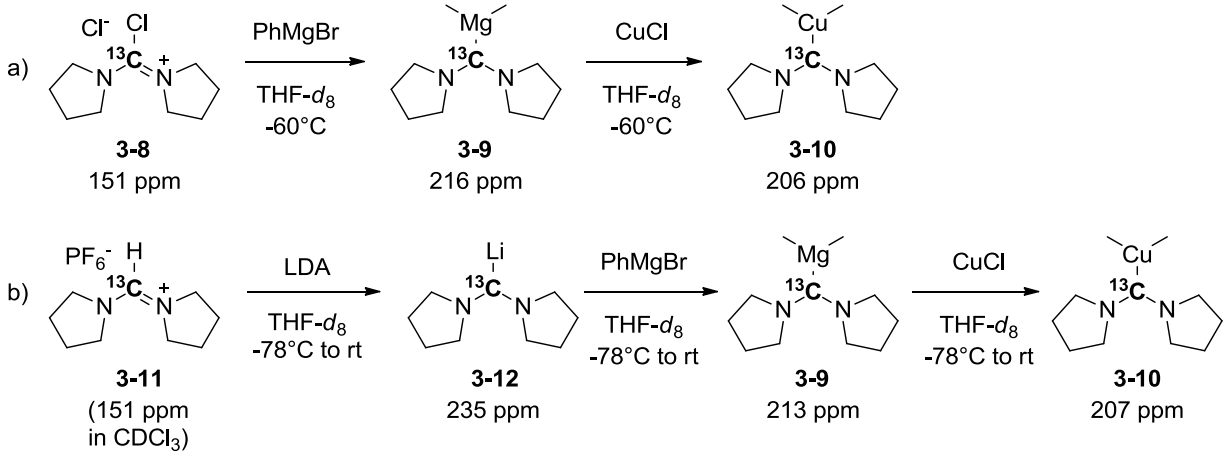
Entry	Substrate **3-1b-f**	Yield (%)	Branched : linear
1		84	≥ 98 : 2
2		97	≥ 98 : 2
3		95	≥ 98 : 2
4		96	≥ 98 : 2
5		93 (with 15 mol% of **3-6**)	≥ 98 : 2

Generation of products containing a quaternary center was obtained in good yields with this methodology (entries 3-5). The *E*/*Z* geometry of the olefin did not interfere with the outcome of the product ratio or with the reactivity (entries 2-4). Protected piperidine **3-1f** required higher catalyst loading, probably due to the nitrogen atom that could coordinate to the copper complex.

^{13}C NMR experiments allowed for the evidence of the generation of an ADC-copper complex with ^{13}C-labeled chloroamidinium **3-8** (Scheme 3-1). When the salt was first mixed with phenylmagnesium bromide, a new downfield signal (δ = 216 ppm) was observed. It then shifted slightly upfield (δ = 206 ppm) once copper(I) chloride was

added to the mixture. The first signal could be attributed to the carbene-magnesium complex **3-9** while the second one could stand for the ADC-copper complex **3-10**.[91, 92]

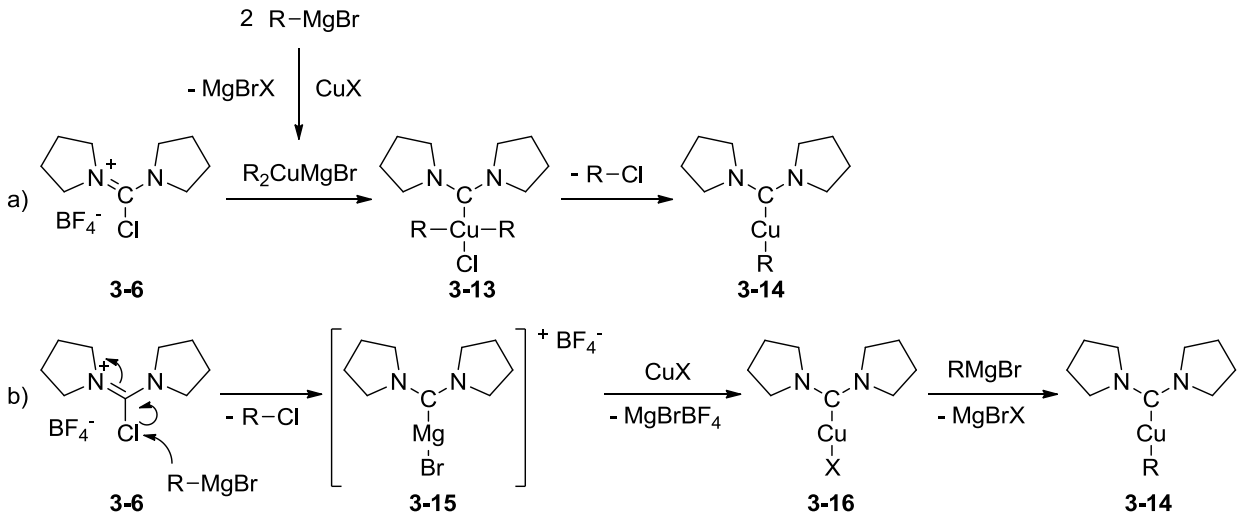
Similar observations could be done by substituting chloroamidinium **3-8** by the corresponding formamidinium **3-11**. After generation of the free carbene in the presence of LDA,[42] the ligand was treated with PhMgBr (δ = 213 ppm). Then copper(I) chloride was added to the mixture and the signal shifted upfield as previously observed (δ = 207 ppm). These experiments confirmed the formation of a carbene that could complex on copper.



Scheme 3-1. Evidence of the formation of the ADC-copper complex a) from chloroamidinium **3-8** and b) from formamidinium **3-11**

Although the mechanism wasn't fully studied, possible approaches could be proposed (Scheme 3-2). A plausible scenario would be the generation of a homocuprate ($R_2CuMgBr$) formed from two equivalents of the Grignard reagent and the copper source.[93] It would then undergo oxidative addition in the presence of the chloroamidinium salt to give a copper(III) adduct. After reductive elimination, it would then form the ADC-organocopper(I) complex. Another mechanism would be first the formation of a carbene-magnesium complex (after magnesium-halide exchange from

the Grignard reagent), followed by transmetalation with the copper salt.[94, 95] Finally, the same ADC-organocopper(I) complex would be obtained after halide displacement with a second equivalent of the Grignard reagent.



Scheme 3-2. Possible mechanisms for the formation of the ADC-organocopper(I)

ADC-Iridium Complex

Design and synthesis of an ADC-iridium complex

The main drawback of the ADC ligands over their cyclic analogues was their degree of freedom due to the free $C_{carbene}$-N rotation. Indeed, as seen previously they could adopt different conformers.[55, 96] It could be suggested that the same complex might have different acitivities depending on the conformer used. To avoid this issue, a new design was conceived where two substituents, one on each nitrogen atom, would have some affinity to each other. Thus, the ligand would become more rigid and would slow down any rotations. An affinity such as π-π stacking interaction between two aromatic rings would be a good choice since the N-C-N bond angle of an ADC ligand is approximately 120°,[42] making the two facing each other. However, the other two

substituents of the nitrogen atoms would have to be sterically demanding enough to avoid formations of undesired conformers of the complex (Figure 3-2).

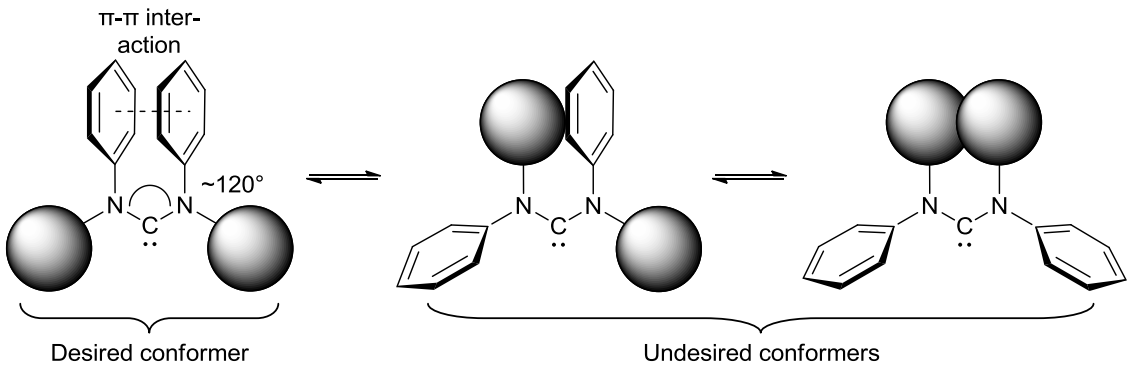
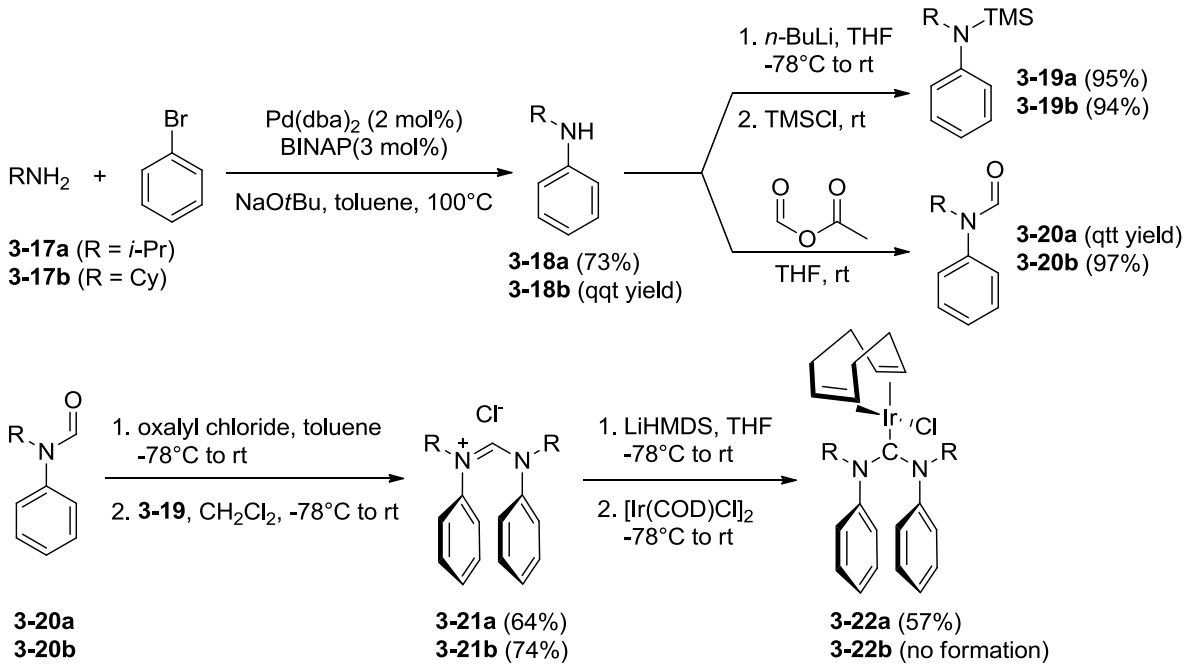


Figure 3-2. Possible conformers of the new acyclic diaminocarbene ligand

From previous attempts of making this type of ADC-metal complexes, it had been noticed that if the bulky group contained a tertiary center alpha to the nitrogen, then the formation of the carbene precursor (formamidinium) wouldn't undergo. Therefore, isopropyl and cyclohexyl substituents as sterically demanding groups have been explored. As for the aromatic moiety, the simple phenyl group was first taken into account and would later be modified.

The synthesis started with a Buchwald-Hartwig coupling between alkylamine **3-17** and bromobenzene. The aniline derivative **3-18** was then divided in two batches. The first one was converted into the corresponding formamidine **3-20** in the presence of DMF. The second batch was silylated in order to favor the formation of the formamidinium (**3-21**). The condensation indeed occurred to afford the chloride salt. Finally, the free carbene was generated in situ with lithium hexamethyldisilazane and then complexed on iridium to afford the desired product **3-22**.



Scheme 3-3. Synthesis of ADC-iridium complex

Surprisingly, the cyclohexyl-substituted iridium complex **3-22b** couldn't be formed. Decomposition of the formamidinium into the amine precursor was observed instead. A simple way to see if the free carbene was formed was to treat the salt with sulfur after deprotonation, which did not take into account the hindrance of the metal. The resulting product would be the corresponding thiourea (Figure 3-3).[97] Once again, the latter wasn't observed but the amine was recovered instead. It could be suggested that once formed, the free carbene wouldn't be stable and would decompose to give the amine back.

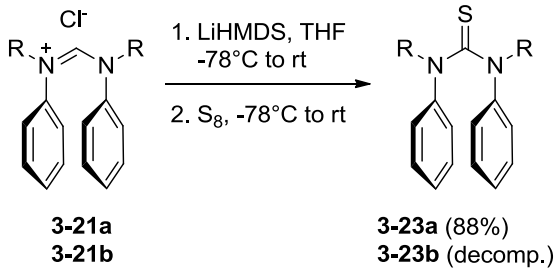


Figure 3-3. Thiourea formation: trapping method of carbene intermediate

An X-ray structure of complex **3-23a** was obtained and as expected, the conformation was *syn* (phenyl groups away from the metal) (Figure 3-4). The N-C-N bond angle was 116.44° wide and the $C_{carbene}$-Ir bond was 2.044Å long. However, the two phenyl groups did not face to each other but instead they would be slightly displaced (the planes orthogonal to each ring formed an angle of 46.3°). This feature (parallel-displaced geometry) was very common in π-π stacking.[98-100] The measured centroid-centroid distance was 3.607Å and the angle formed between two vectors – one normal to one of the rings and the other one passing through the two centroids – was 29.02°. These data were in agreement with Janiak's study on the π-π stacking in metal complexes with aromatic nitrogen-containg ligands.[100] He calculated these same data for more than 4,800 structures and he observed a maximum peak in the distribution at 3.8Å and 27°. The values found for complex **3-23a** were close to Janiak's ones and could therefore suggest a possible stacking with a parallel-displaced geometry.

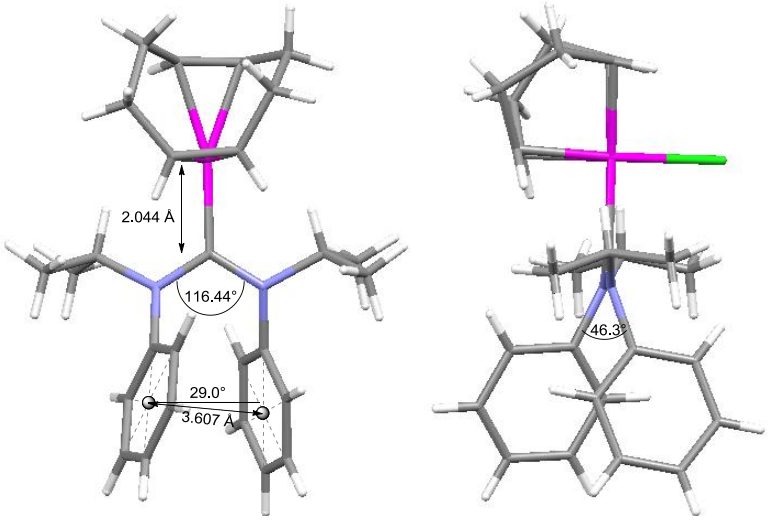


Figure 3-4. X-ray structures of complex **3-23a**

The only other X-ray structure of an ADC-iridium complex was obtained by Bielawski in 2010 (Figure 3-5).[55] The conformation of his ligand was also *syn*: the two

mesityl groups being away from the metal center. However, the $C_{carbene}$-Ir bond was longer than the one of **3-23a** (2.061(4)Å) suggesting a possible weaker bond. Also the N-C-N bond angle was wider (118.9(4)°), this could be due to less π- π interaction or more hindrance between the two mesityl groups.

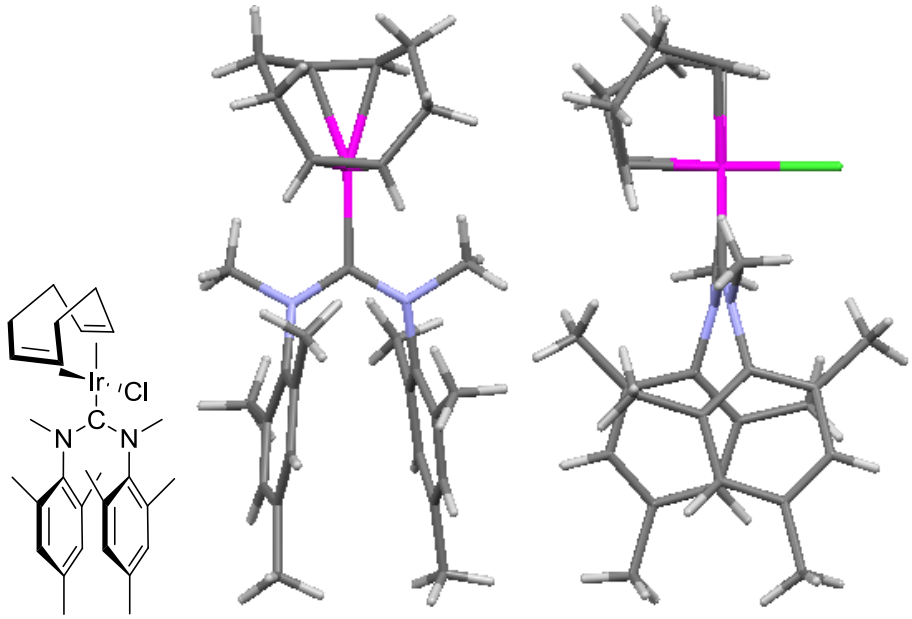
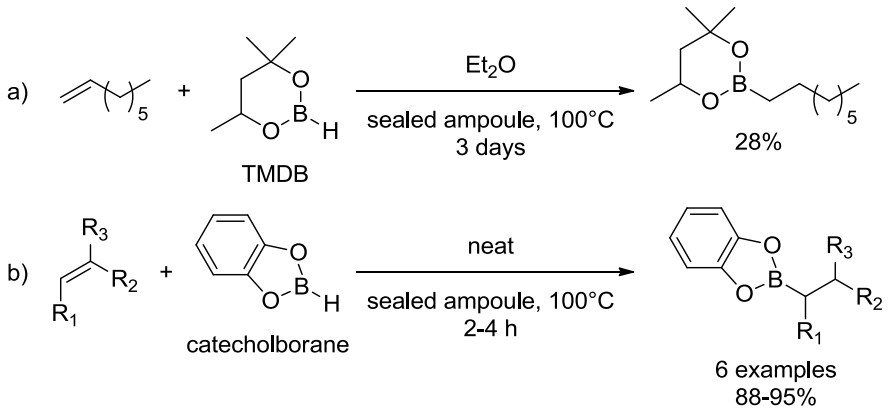


Figure 3-5. X-ray structure of Bielawski's ADC-iridium complex

With the isopropyl-substituted metal complex in hands, iridium-catalyzed reactions could be tested.

Hydroboration of alkenes

Hydroboration of alkenes with dioxaborinane derivatives have first been reported by Woods in 1966 with TMDB (4,4,6-trimethyl-1,3,2-dioxaborinane).[101] He performed the hydroboration on 1-octene and he obtained the terminal product as the sole regioisomer in 28% yield (Scheme 3-4 a)). Brown also hydroborated mono- and disubstituted alkenes (terminal or not) with catecholborane in better yields (Scheme 3-4 b)).[102]



Scheme 3-4. Hydroboration of alkenes by a) Woods and b) Brown

For both examples high temperatures were required (100°C) and the terminal products were obtained due to the sterics of the boration reagents and to the electronic effect of the alkene.

In order to use milder conditions, the reaction could be catalyzed by transition metals. Indeed, in 1975, Kono showed the capability of Wilkinson's catalyst to undergo oxidative addition with catecholborane, by isolating the resulting product (Figure 3-6).[103]

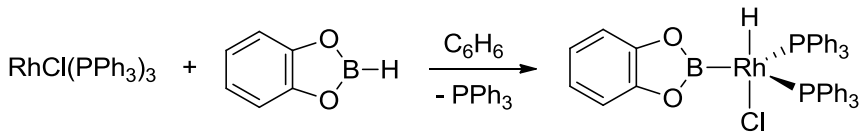


Figure 3-6. Oxidative addition of catecholborane to Wilkinson's reagent

Then in 1985, Nöth first reported the catalytic activity of Wilkinson's reagent in the hydroboration of 1-octene with catecholborane.[104] The desired product was obtained in 78% yield, in only 25 min, and at room temperature (Figure 3-7). Besides, ketone and nitrile functional groups were tolerated through the process.

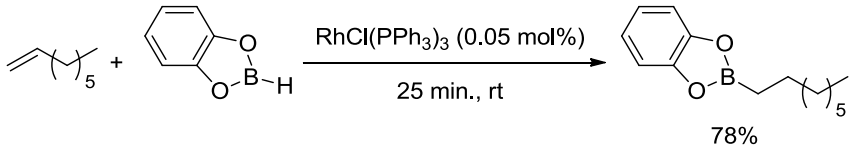


Figure 3-7. First rhodium-catalyzed hydroboration

While the regioselectivity might be identical whether a metal was used or not, the mechanism did not remain the same. Indeed, Nöth porposed a mechanism that had later been confirmed by Evans with extra study (Figure 3-8).[104, 105] After oxidative addition of Wilkinson's catalyst on catecholborane, the olefin would bind to the metal. Then followed a hydride migration from rhodium to the alkene. Finally, reductive elimination gave the hydroborated product with regeneration of the catalyst.

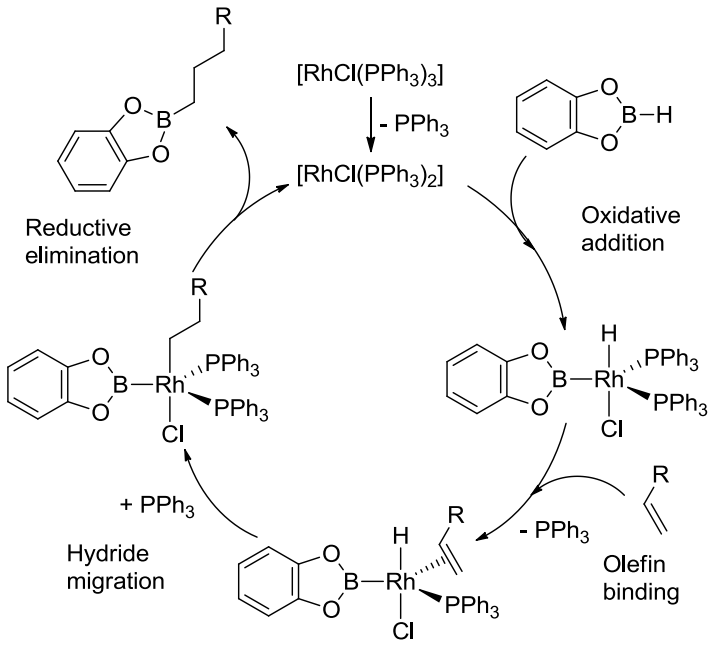


Figure 3-8. Mechanism of rhodium-catalyzed hydroboration of terminal olefins

Evans went more in depth about the mechanistic study and proved by isotope labeling that it was indeed a hydride (and not a boron) migration. He also concluded that the reductive elimination could not occur from a secondary alkyl group but only from a primary one. Hence, the terminal olefin was always functionalized at the primary carbon. Besides, he also studied the hydroboration of styrene. In this particular case, the regioselectivity was inverted, that is to say, the secondary carbon was bound to the

boron. This was explained by the migration of the hydride exclusively at the primary carbon, thus generating a benzylic alkyl rhodium complex.

The regioselectivity outcome of the hydroboration of styrene was also dependent on the boron reagent employed. Indeed, when Miyaura used more sterically demanding pinacolborane, he obtained a 1/0.5 mixture of the linear/branched products in the presence of the Wilkinson's catalyst.[106] When he catalyzed the same reaction with $[Ir(cod)Cl]_2$ in the presence of a bidentate phosphine (dppm, dppe, or dppb) or with some cationic iridium complexes, he exclusively obtained the linear product.

It was then interesting to compare the behavior of the newly made iridium complex **3-23a**. Unfortunately, despite the low reactivity of the catalyst, the regioselectivity was similar as of the Wilkinson's reagent, with a linear/branched ratio of 1/0.56 (Figure 3-9). When compared with other NHC- and ADC-iridium complexes, IMesIr(cod)Cl was the most regioselective (linear product only). Besides, it didn't seem that the steric or the electronic effects of the carbene ligand had an impact on the product distribution as they gave different results.

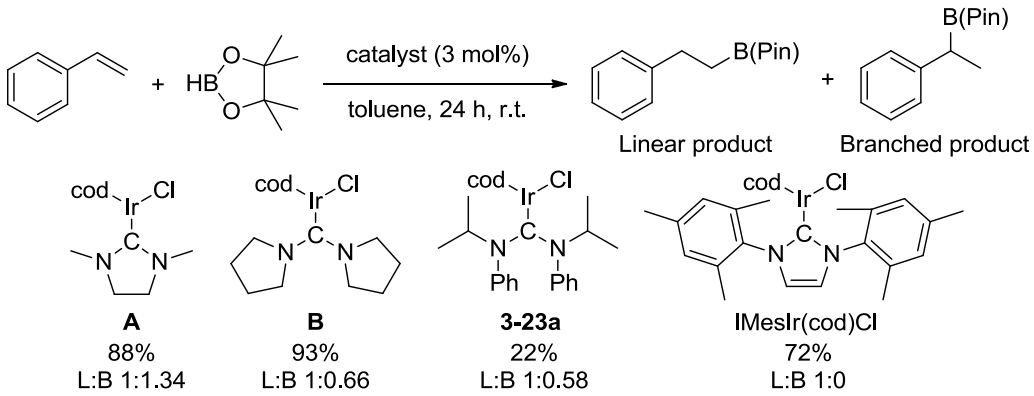


Figure 3-9. Iridium-catalyzed hydroboration of styrene

Chiral Acyclic Diaminocarbene Precursors

The use of chiral acyclic diaminocarbenes as ligands in the asymmetric catalysis hasn't been widely explored. Indeed, while the ADCs were thought to be more σ-donor towards the metal than the NHC analogues, they still remained less rigid. The free rotation around the $C_{carbene}$-N bond allowed more degrees of freedom which could cause a decrease in the efficiency towards the stereoselectivity of the corresponding ligand.

Original Design of a Chiral Acyclic Diaminocarbene

The original thought was to form an ADC ligand containing a C_2-symmetric disubstituted pyrrolidine (Figure 3-10). Hence, the rotation around the $C_{carbene}$-N bond would not have any effect since there would always be a chiral center (with the same absolute configuration) pointing towards the metal center. Such a geometry would block two quadrants diametrically opposed, hence giving a C_2 symmetry to the ligand.

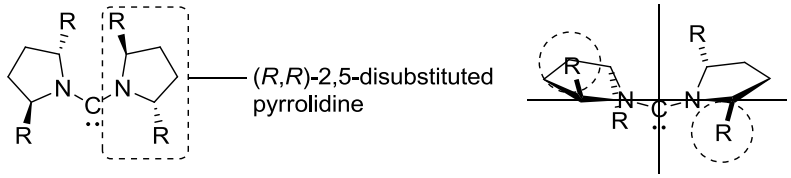


Figure 3-10. Original design of a chiral ADC ligand

The ADC-metal complex would either be generated 1) from deprotonation of the formamidinium **3-25** and complexation of the newly formed carbene on the metal or 2) from metal-halide exchange of the chloroamidinium **3-26** (Figure 3-11). Both salts would be obtained from the chiral 2,5-disubstituted pyrrolidine **3-27**.

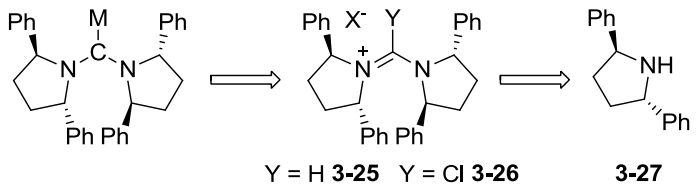
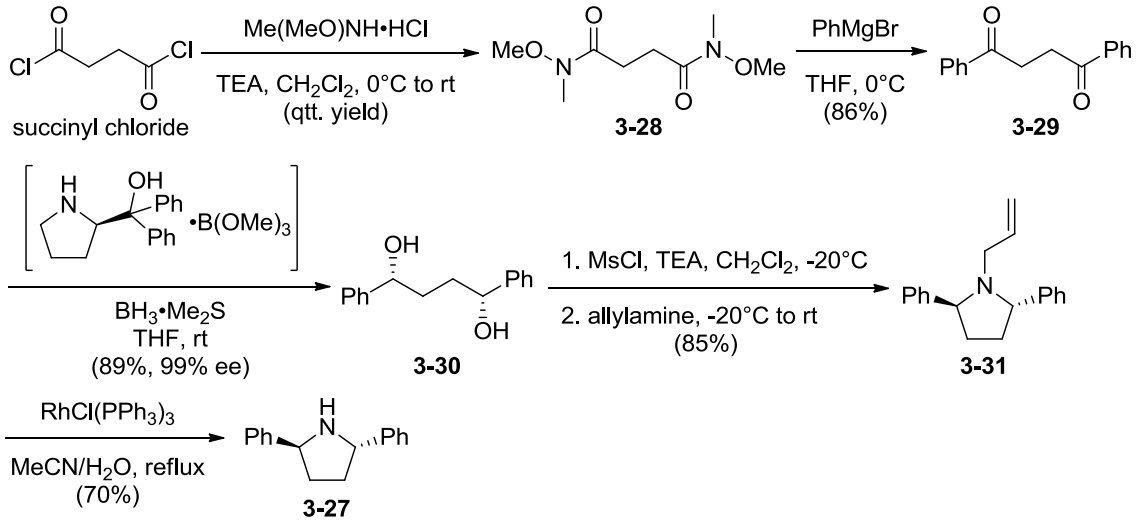


Figure 3-11. Preparation of the chiral ADC-metal complex

The chiral pyrrolidine **3-27** was prepared according to known procedures (Scheme 3-5).[107, 108] First, succinyl chloride was converted to the corresponding diphenyl ketone **3-29** in the presence of phenylmagneium bromide via the corresponding Weinreb amide **3-28**. After CBS reduction into diol **3-30**, the protected pyrrolidine **3-31** could be obtained by activation of the alcohols and S_N2 reactions with allylamine. Wilkinson reagent allowed the formation of chiral pyrrolidine **3-27**.



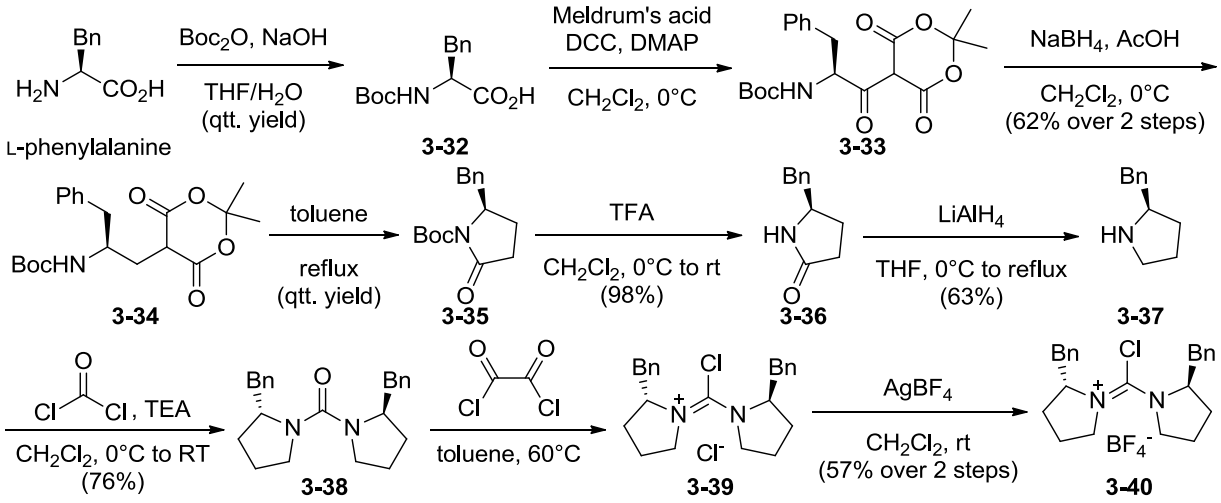
Scheme 3-5. Preparation of the chiral pyrrolidine **3-27**

Unfortunately, the formation of formamidinium **3-25** or of the chloroamidinium precursor, the corresponding urea, was not successful. This might be due to the high hindrance of the product. Therefore, the original design was revisited and a simpler one was then investigated with only one chiral center on each pyrrolidine moiety.

New Design of a Chiral Acyclic Diaminocarbene

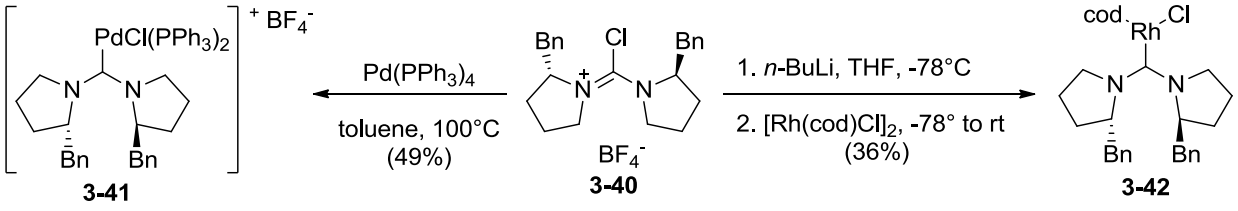
The chiral monosubsituted pyrrolidine **3-37** was synthesized from known procedures.[49, 109, 110] It started with the *N*-Boc protection of L-phenylalanine, to allow condensation of the carboxylic part with the Meldrum's acid to give **3-33** (Scheme 3-6). The ketone moiety was then completely reduced to a methylene group in the presence

of sodium borohydride. After a reflux in toluene, the lactam **3-35** was formed via decarboxylation and release of acetone. **3-35** was then deprotected with TFA in methylene chloride to give the free lactam **3-36** which was next reduced to the corresponding amine **3-37** without erosion of the enantiopurity during the whole synthesis. The α-substituted amine was then treated with phosgene to give urea **3-38**. The chloroamidinium **3-39** was then obtained by subjecting the urea in the presence of oxalyl chloride. An anion exchange was subsequentially performed with $AgBF_4$. It's been noted the BF_4^- counter ion gave more stability to the complex than the chloride one.[49]



Scheme 3-6. Synthesis of chloroamidinium **3-40**

At this stage, chloroamidinium salt was complexed on either palladium(0) by oxidative addition or on rhodium via formation of the free carbene (Scheme 3-7).[49, 111]



Scheme 3-7. Formation of chiral ADC-Pd **3-41** and ADC-Rh **3-42** complexes

Once the ADC-palladium complex **3-41** was obtained, it was then tested for the asymmetric Suzuki reaction. This coupling was of interest since ADC ligands were strong σ-donors whom feature favored the oxidative addition of the catalyst with aryl halide.[112] Besides, these ligands brought more hindrance around the metal sphere, due to their wider N-C-N angle (in respect to NHCs), which could make the reductive elimination easier. These two properties were well illustrated by Thadani as he obtained the desired products of the coupling reactions in good to excellent yields in the presence of a simple ADC ligand (Scheme 1-14).[50] As expected, the activity of the ADC-Pd complex **3-41** was good (85%), but unfortunately the enantioselectivity was nearly inexistent (Scheme 3-12).

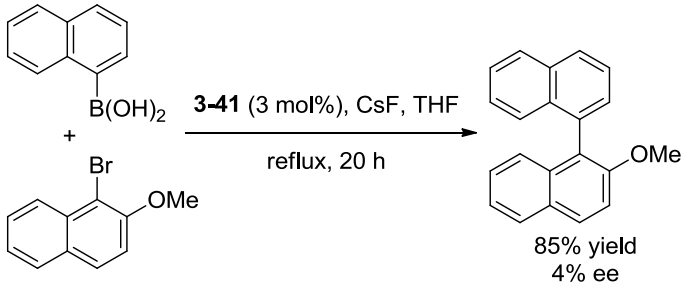


Figure 3-12. ADC-palladium catalyzed Suzuki-Miyaura coupling reaction

With the ADC-rhodium complex **3-42**, the 1,2-addition reaction of 1-naphthylboronic acid to *o*-anisaldehyde was tested (Figure 3-13). Again, while the activity of the complex was good in low catalyst loading, the enantioselectivity wasn't not observed.

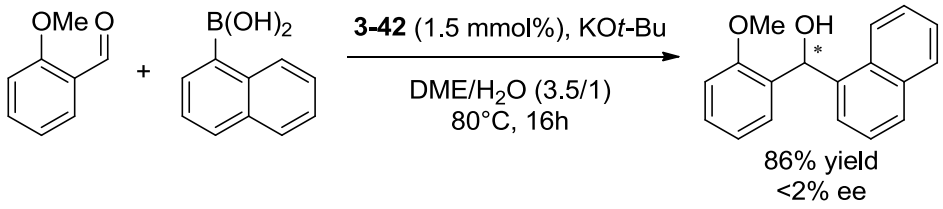


Figure 3-13. ADC-rhodium catalyzed 1,2-addition reaction

The lack of enantioselectivity might be due to too much freedom around the $C_{carbene}$-N bond. The expected conformer **A** might not be the most stable (Figure 3-14). However, while conformer **B** with the two chiral centers at the back (away from the metal) would be very sterically demanding, it would be nonetheless possible that only one of them remained at the back with the other one pointing towards the front (conformer **C**). This conformation could be the result of a lack of enantioselectivity for both Suzuki coupling and 1,2-addition in these conditions.

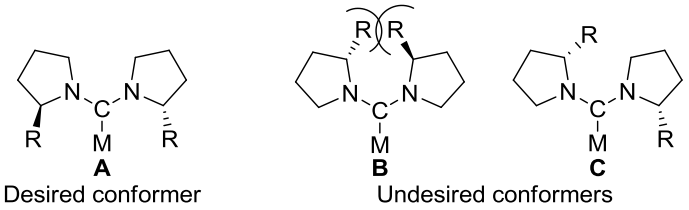


Figure 3-14. Undesired conformations of the ADC metal complexes

Experimental Section

ADC-Copper Catalyzed Allylic Alkylation

Typical procedure for allylic alkylation

To a flame-dried Schlenk flask were added CuTC (5 mol%), chloroamidinium salt **3-6** (5 mol%) and 1 mL of diethyl ether. To this solution was added an ethylmagnesium bromide (0.22 mmol in Et_2O) at 0°C. The mixture reaction was stirred for 5 min at 0°C. Then a solution of substrate **3-1** (0.15 mmol) in 1 mL of Et_2O was added over a 15 min period. After 1 hour, the reaction was quenched by a saturated aqueous NH_4Cl solution and extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to give a pure product **3-4**.

Characterizations of products 3-4a-f

1-((2-ethylbut-3-enyloxy)methyl)-4-methoxybenzene (3-4a). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.20 - 7.37 (m, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.54 - 5.79 (m, 1H), 4.98 - 5.23 (m, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.36 (d, *J* = 6.4 Hz, 2H), 2.12 - 2.42 (m, 1H), 1.45 - 1.71 (m, 1H), 1.13 - 1.37 (m, 1H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 159.1, 140.0, 130.7, 129.1, 115.5, 113.7, 73.2, 72.6, 55.2, 45.7, 24.0, 11.4. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{14}H_{20}O_2$, 220.1463; found, 220.1477.

2-ethylbut-3-enyl 4-methoxybenzoate (3-4b). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.91 (d, *J* = 8.78 Hz, 2H), 6.83 (d, *J* = 9.06 Hz, 2H), 5.62 (ddd, *J* = 17.06, 10.40, 8.21 Hz, 1H), 5.00 - 5.09 (m, 2H), 4.15 (dd, *J* = 6.51, 1.98 Hz, 2H), 3.77 (s, 3H), 2.25 - 2.41 (m, 1H), 1.44 - 1.60 (m, 1H), 1.23 - 1.39 (m, 1H), 0.86 (t, *J* = 7.36 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 166.52, 163.50, 139.18, 131.76, 123.07, 116.68, 113.79, 67.37, 55.61, 45.13, 24.23, 11.61. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{14}H_{18}O_3$, 257.1148; found, 257.1142.

1-(2-ethylbut-3-enyl)-4-methoxybenzene (3-4c). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.06 (d, *J* = 9 Hz, 2H), 6.81 (d, *J* = 9 Hz, 2H), 5.47 - 5.72 (m, 1H), 4.73 - 5.04 (m, 2H), 3.79 (s, 3H), 2.43 - 2.70 (m, 2H), 2.05 - 2.27 (m, 1H), 1.36 - 1.52 (m, 1H), 1.17 - 1.36 (m, 1H), 0.87 (t, *J* = 8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 157.9, 142.6, 133.0, 130.3, 114.8, 113.7, 55.4, 47.7, 40.8, 27.0, 11.9. . HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{13}H_{18}O$, 191.1430; found, 191.1436.

3-ethyl-3,7-dimethylocta-1,6-diene (3-4d). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 5.71 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.05 - 5.15 (m, 1H), 4.84 - 5.02 (m, *J* = 15.9, 11.0, 1.6 Hz, 2H), 1.82 - 1.94 (m, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.21 - 1.34 (m, 4H), 0.96 (s, 3H), 0.86 - 0.92 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 147.5, 130.9, 125.2, 111.3, 40.9,

32.0, 30.2, 25.7, 24.0, 22.6, 17.6, 14.1. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{12}H_{22}$, 166.1722; found, 166.1719.

4-ethyl-1-tosyl-4-vinylpiperidine (3-4f). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.58 (m, *J* = 8 Hz, 2H) 7.26 (m, *J* = 8 Hz, 2H), 5.36 (dd, *J* = 18, 11 Hz, 1H), 5.04 (d, *J* = 11 Hz, 1H), 4.77 (d, *J* = 18 Hz, 1H), 3.17 - 3.35 (m, 2H), 2.55 - 2.71 (m, 2H), 2.38 (s, 3H), 1.59 - 1.76 (m, 2H), 1.41 - 1.59 (m, 2H), 1.22 (q, *J* = 7 Hz, 2H), 0.68 (t, *J* = 7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 143.4, 133.8, 129.8, 127.8, 115.1, 42.9, 38.1, 34.1, 33.6, 21.8, 7.7. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{16}H_{23}NO_2S$, 294.1522; found, 294.1499.

ADC-Iridium Complexes

Syntheses of iridium complexes

***N*-isopropylaniline (3-18a).** To an oven-dried high pressure flask, were added $Pd(dba)_2$ (0.22 g, 0.38 mmol) and (±)-BINAP (0.35 g, 0.57 mmol) in toluene (18 mL). The solution was stirred for 30 minutes under a nitrogen atmosphere. Then to the reaction mixture were added bromobenzene (2 mL, 19.0 mmol), isopropylamine (1.8 mL, 20. 9 mmol), sodium *tert*-butoxide (2.56 g, 26.6 mmol), and toluene (18 mL). The solution was stirred for 2 days at 100°C. The mixture was filtered over a plug of Celite and rinsed with ethyl acetate. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate: 3/1) to give 1.88 g (73%) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.16 (t, *J* = 7.7 Hz, 2H), 6.66 (tt, *J* = 1.3, 7.3 Hz, 1H), 6.58 (td, *J* = 1.0, 7.7 Hz, 2H), 3.62 (spt, *J* = 6.2 Hz, 1H), 3.42 (br s, 1H), 1.20 (dd, *J* = 1.0, 6.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 147.7, 129.5, 117.1, 113.4, 44.4, 23.2. IR (cm^{-1}): 3401, 2967, 1604, 1508, 1318, 1256, 1179, 748, 693. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_9H_{13}N$, 136.1121; found, 136.1125.

***N*-isopropyl-1,1,1-trimethyl-*N*-phenylsilanamine (3-19a).** To a flame-dried Schlenk flask, was added *N*-isopropylaniline (1.0 g, 7.40 mmol) in tetrahydrofuran (10 mL). The solution was cooled to -78°C and a 1.6 M solution of *n*-butyl lithium in hexane (5.5 mL, 8.88 mmol) was added dropwise. Then, the reaction mixture was slowly warmed to room temperature and stirred for 1 hour. Next, chlorotrimethylsilane (1.4 mL, 1.21 g) was added dropwise and the reaction was stirred at room temperature for 5 days. Any volatiles were evaporated under reduced pressure and diethyl ether was added to the residual oil forming a while solid which was then filtered over a plug of Celite. The filtrate was concentrated under reduced pressure and the crude product was purified by distillation giving 1.41 g (95%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.27–7.21 (m, *J* = 7.4 Hz, 2H), 7.12 (s, 1H), 7.01 (dd, *J* = 1.2, 8.4 Hz, 2H), 3.59 (spt, *J* = 6.7 Hz, 1H), 1.05 (d, *J* = 6.7 Hz, 6H), 0.06 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 145.4, 132.2, 128.2, 124.4, 48.8, 24.0, 0.9. IR (cm^{-1}): 2966, 1597, 1490, 1250, 1045, 918, 833, 703. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{12}H_{21}NSi$, 208.1516; found, 208.1523.

Synthesis of *N*-isopropyl-*N*-phenylformamide (3-20a). To a flame-dried Schlenk flask, were added *N*-isopropylaniline (1.0 g, 7.40 mmol) in tetrahydrofuran (10 mL) and acetic formic anhydride (0.98 g, 11.10 mmol) dropwise. The solution was stirred for 2 days at room temperature and then quenched with a 1 M sodium hydroxide aqueous solution at 0°C. The aqueous phase was extracted with diethyl ether and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by distillation to give 1.20 g (99%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): Major isomer: 8.17 (s, 1H), 7.46–7.34 (m, 3H), 7.19–7.13 (m, 2H), 4.80 (spt, *J* = 6.8 Hz, 1H), 1.20 (d, *J* = 6.9 Hz,

6H); Minor isomer: 8.45 - 8.41 (m, 1H), 7.45 –7.35 (m, 3H), 7.19–7.14 (m, 2H), 4.11 (spt, *J* = 6.8 Hz, 1H), 1.28 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): Major isomer: 162.5, 138.4, 129.7, 129.0, 128.2, 45.8, 21.0; Minor isomer: 162.5, 129.2, 129.1, 128.0, 51.5, 22.7. IR (cm^{-1}): 2977, 2936, 2876, 1669, 1595, 1497, 1370, 1296, 1257, 1120, 703. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{10}H_{13}NO$, 164.1070; found, 164.1064.

Bis(*N*-phenyl-*N*-isopropyl)amidinium chloride (3-21a). To a flame-dried Schlenk flask, were added formamide (**3-20a**) (1.0 g, 6.13 mmol) in toluene (6.1 mL) and oxalyl chloride (0.80 mL, 9.44 mmol) dropwise, at -78°C. After 20 min of stirring, the yellow solution was stirred at room temperature for 2 hours. Next, any volatiles were evaporated under reduced pressure. The resulting yellow solid was then dissolved in methylene chloride (4.1 mL) and the solution was cooled to -78°C. To the reaction mixture was added dropwise a solution of protected amine (**3-19a**) (1.27 g, 6.13 mmol) in methylene chloride (2 mL). The reaction was slowly warmed to room temperature and stirred overnight. Any volatiles were evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, hexanes/ethyl acetate: 1/1 then methylene chloride/methanol 97/3). The solid was then dissolved in a minimum amount of methylene chloride and precipitated with diethyl ether which was rinsed several times with diethyl ether to give 1.24 g (64%) of a white solid. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 10.52 (s, 1H), 7.10–7.05 (m, 2H), 7.04–6.99 (m, 4H), 6.73–6.69 (m, 4H), 5.12 (quin, *J* = 6.6 Hz, 2H), 1.25 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 157.2, 134.1, 129.5, 129.1, 129.1, 61.0, 21.9. IR (cm^{-1}): 3420, 3352, 1636, 1590, 1503, 1453, 1110, 700. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{25}N_2$, 281.20; found, 281.2020.

Iridium complex (3-22a). To a flame-dried Schlenk flask, was added amidinium (**3-21a**) (75 mg, 0.24 mmol) in tetrahydrofuran (3 mL). The reaction mixture was cooled to -78°C and a 1 M solution of LiHMDS in tetrahydrofuran (026 mL, 0.26 mmol) was added dropwise. The flask was warmed to room temperature and stirred for 30 minutes. Then, $[Ir(cod)Cl]_2$ complex (80 mg, 0.12 mmol) was added at -78°C. The solution was slowly warmed to room temperature and stirred overnight. Any volatiles were evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/ethyl acetate: 4/1) to give iridium complex (**3-22a**) as a yellow solid. Crystals for X-ray analysis were obtained by slow diffusion of hexanes in highly concentrated solution of the iridium complex in DCM. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.05–6.83 (m, 6 H), 6.73 - 6.54 (m, 4 H), 6.22 (d, *J* = 7.7 Hz, 2 H), 4.67–4.55 (m, 2 H), 3.38–3.25 (m, 2 H), 2.36–2.21 (m, 4 H), 1.85–1.75 (m, 2 H), 1.75–1.64 (m, 2 H), 1.19 (d, *J* = 6.7 Hz, 6 H), 1.09 (d, *J* = 6.7 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 143.9, 129.8, 129.2, 128.6, 128.3, 126.0, 82.6, 59.5, 52.3, 33.5, 29.6, 22.5, 22.2. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{27}H_{34}IrN_2$, 579.2347; found, 579.2374.

Iridium complex A: In a glove box, a 10 mL Schlenk flask was charged with chloroamidinium chloride (0.10 g, 0.36 mmol). Outside the glove box, was added THF (2 mL) and the solution was cooled to -78°C. A solution of *n*-BuLi (1.6M in hexanes, 0.24 mL, 0.38 mmol) was slowly added and the reaction mixture was stirred over 1 hour at that same temperature. Finally complex $[Ir(cod)Cl]_2$ (0.12 g, 0.18 mmol) was added and the solution was stirred overnight at room temperature. Any volatiles were evaporated under reduced pressure and the crude was purified by column chromatography (silica gel, hexanes/EtOAc: from 2/1 to 1/1) to give 0.13 g (73%) of a

yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 4.57 - 4.45 (m, 2 H), 3.55 (m, 4 H), 3.41 (s, 6 H), 3.04 - 2.93 (m, 2 H), 2.24 - 2.10 (m, 4 H), 1.79 - 1.68 (m, 2 H), 1.66 - 1.54 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 207.9, 84.9, 52.0, 33.6, 29.5.

Iridium complex B: The same procedure as above was used starting from 2-chloro-1,3-dimethylimidazolinium chloride to give complex **3-X** as a yellow solid (17% yield). ^{1}H NMR (500 MHz, $CDCl_3$ δ): 4.57 (br. s., 2 H), 4.42 - 4.34 (m, 2 H), 4.27 (br. s., 2 H), 3.48 (br. s., 4 H), 2.94 - 2.85 (m, 2 H), 2.24 - 2.09 (m, 4 H), 1.88 (br. s., 8 H), 1.69 - 1.60 (m, 2 H), 1.58 - 1.49 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$, δ):211.9, 81.6, 51.9, 33.5, 29.5.

Iridium complex [IMesIr(cod)Cl]: The same procedure as for complex **3-22a** was used starting from IMesH·Cl to afford [IMesIr(cod)Cl] as a bright orange solid (quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$ δ): 7.40 - 7.21 (m, 2 H), 7.12 - 6.92 (m, 4 H), 4.30 - 4.06 (m, 2 H), 3.08 - 2.91 (m, 2 H), 2.36 (s, 12 H), 2.17 (s, 6 H), 1.84 - 1.63 (m, 4 H), 1.42 - 1.17 (m, 4 H).

Typical procedure for the hydroboration

To a flame-dried Schlenk flask, were added iridium complex **3-23a** (18.5 mg, 0.03 mmol), pinacolborane (0.174 µL, 1.2 mmol), freshly distilled styrene (115 µL, 1.0 mmol) and toluene (3 ml). The mixture was then stirred at room temperature over 24 hours. The reaction was quenched with methanol (1 mL) and water (3 mL). The product was extracted with diethyl ether, and dried over $MgSO_4$. Purification on column chromatography (Silica gel, hexanes/ethyl acetate: 90/10) gave 70 mg of the product (30%) as a light yellow oil. Linear product: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.33-7.12 (m, 5 H), 2.84-2.72 (t, *J* = 8.1 Hz, 2 H), 1.25 (s, 12 H), 1.20 - 1.14 (t, *J* = 8.2 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 144.6, 128.5, 128.4, 125.5, 83.3, 30.2, 25.0. Branched

product: ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.31-7.09 (m, 5 H), 2.43 (q, *J* = 7.6 Hz, 1 H), 1.33 (d, *J* = 7.6 Hz, 3 H), 1.21 (s, 6 H), 1.20 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 144.1, 128.5, 128.0, 125.7, 83.5, 29.3, 20.9, 11.7.

NMR spectra

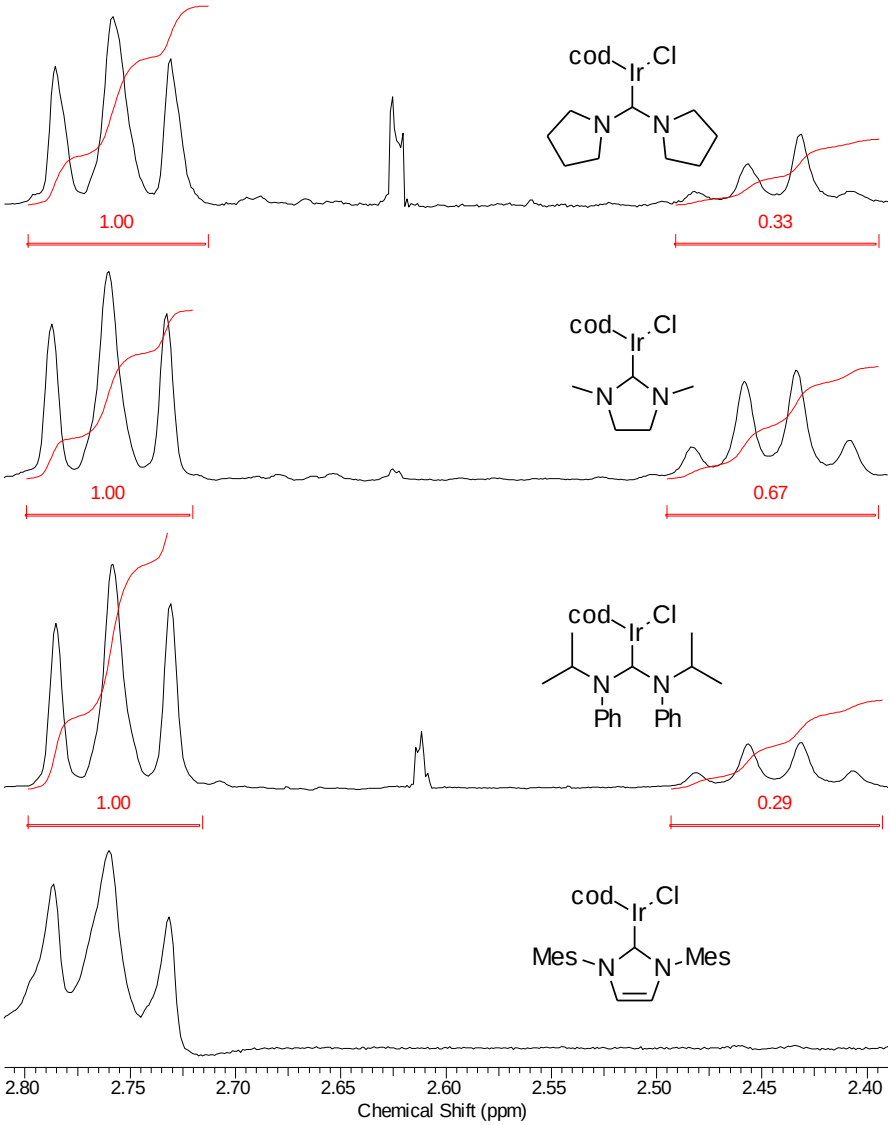


Figure 3-15. NMR spectra of the hydroboration product

Chiral Acyclic Diaminocarbene Metal Complexes

Synthesis of chloroamidinium salt 3-40

Bis((*R*)-2-benzylpyrrolidin-1-yl)methanone (3-38). To a flame-dried Schlenk flask, were added pyrrolidine **3-37** (1.18 g, 7.34 mmol) and triethylamine (3.0 mL, 21.5 mmol) in methylene chloride (15 mL). The solution was cooled to 0°C and a 20% solution of phosgene in toluene (2.0 mL, 3.80 mmol) was added dropwise. The reaction mixture was stirred 40 minutes at 0°C and then overnight at room temperature. The solution was quenched with water and the aqueous phase was extracted with methylene chloride. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate: 3/2) to afford 0.97 g (76%) of a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.47–7.09 (m, 10 H), 4.28 (dd, *J* = 3.4, 6.3 Hz, 2 H), 3.45–3.05 (m, 6 H), 2.60 (dd, *J* = 8.8, 12.9 Hz, 2 H), 1.90 (td, *J* = 2.6, 5.7 Hz, 2 H), 1.84–1.44 (m, 8 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 161.6, 139.4, 129.9, 128.3, 126.2, 59.6, 50.2, 40.8, 30.7, 25.5. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{23}H_{28}N_2O$, 349.2274; found, 349.2279.

(*R*,*Z*)-2-benzyl-1-(((*R*)-2-benzylpyrrolidin-1-yl)chloromethylene)pyrrolidin-1-ium tetrafluoroborate (3-40). To a flame-dried Schlenk flask, were added urea **3-38** (0.22 g, 0.62 mmol) and oxalyl chloride (63 µL, 0.74 mmol) in toluene (3 mL). The reaction mixture was heated to 50°C and stirred overnight. The solution was cooled to room temperature and the toluene resting on top of the precipitate was removed with a syringe. The oily residue was washed twice with diethyl ether, dissolved in copious amounts of tetrahydrofuran, and precipitated with pentanes as a slightly orange solid.

Any volatiles were evaporated under reduced pressure, then methylene chloride (4 mL) and silver(I) tetrafluoroborate (0.12 g, 0.62 mmol) were added to the solid. The reaction was stirred for 1 h. After this time, the methylene chloride was removed by filtration and transferred into a flame-dried Schlenk flask under an argon atmosphere, and the solids were washed with methylene chloride, collecting the organics. Volatiles were removed, and the solid was dissolved with generous amounts of tetrahydrofuran. The product was precipitated with diethyl ether, resulting in 0.16 g (57%) of a pale brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.34–7.11 (m, 10 H), 4.48 (br s, 2 H), 3.82 (br s, 4 H), 3.08 (dd, *J* = 3.5, 14.6 Hz, 2 H), 2.82 (br s, 2 H), 2.11 (br s, 4 H), 2.04–1.82 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 152.9, 136.2, 129.9, 129.5, 129.1, 128.9, 128.6, 127.5, 67.4, 56.3, 40.3, 30.4, 24.9. HRMS (*m*/*z*): $[M - BF_4]^+$ calcd for $C_{23}H_{28}BClF_4N_2$, 367.1936; found, 367.1973.

Syntheses of ADC-metal complexes 3-41 and 3-42

Chlorobis ((*R*)-2-benzylpyrrolidinyl)methylidenebistriphenylphosphinepalladium tetrafluoroborate (3-41). To a flame-dried Schlenk flask, were added chloroamidinium **3-40** (50 mg, 0.11 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.13 g, 0.11 mmol) in toluene (8 mL). The solution was heated for 3 hours at 100°C. The mixture was allowed to cool to room temperature and any volatiles were evaporated under reduced pressure. Pentane was added to the resulting solid, which was stirred for 1 h before being decanted. Methylene chloride was used to dissolve the product, and insoluble salts were filtered off. Pentane was layered on top of the filtrate to purify the product by recrystallization (57 mg, 48%). ^{1}H NMR (300 MHz, CD_2Cl_2, δ): 7.83–7.63 (m, 5 H), 7.54 (br s, 10 H),

7.50–7.31 (m, 6 H), 7.31–7.01 (m, 17 H), 7.01–6.80 (m, 4 H), 5.49 (dt, *J* = 5.6, 11.5 Hz, 2 H), 4.48–4.28 (m, 2 H), 3.85–3.66 (m, 2 H), 2.96 (dd, *J* = 4.8, 13.9 Hz, 2 H), 2.72–2.49 (m, 2 H), 2.13–1.96 (m, 1 H), 1.96–1.81 (m, 2 H), 1.81–1.52 (m, 3 H), 1.43 (br s, 1 H), 1.34–1.01 (m, 3 H). ^{13}C NMR (75 MHz, CD_2Cl_2, δ): 185.8, 137.1, 135.3, 134.7, 134.3, 132.4, 131.6, 130.2, 129.1, 128.8, 128.5, 126.8, 71.5, 54.3, 40.0, 25.8, 22.8. HRMS (*m*/*z*): $[M - BF_4]^+$ calcd for $C_{59}H_{58}BClF_4N_2P_2Pd$, 997.2810; found, 997.2817.

Chloro(η^4-1,5-cyclooctadiene)bis((*R*)-2-benzylpyrrolidinyl)-methylidenerhodium(I) (3-42). To a Schlenk flask in a glovebox was added 100 mg (0.364 mmol) of bis(pyrrolidinyl)chloroamidinium tetrafluoroborate (**3-40**), and the flask was connected to a Schlenk line outside the glovebox. THF (2 mL) was added, and the suspension was cooled to -78°C with a dry ice/acetone bath. After cooling, 2.5 M *n*-BuLi in hexanes (153 µL) was added. After 5 min, the suspension turned to a clear and slightly yellowish solution upon formation of carbene. After stirring for 1 h at -78°C, $[Rh(cod)Cl]_2$ (89.6 mg, 0.182 mmol) was added, and the reaction slowly warmed to room temperature. Stirring at room temperature proceeded for 12 h, at which point, solvent was evaporated. To remove any remaining $[Rh(cod)Cl]_2$, the product was purified by chromatography on a very short pad of silica gel. Columns were run starting with a mixture of 2:1 hexanes/ethyl acetate and proceeding to pure ethyl acetate. The complexes showed very slight decomposition on silica gel, so the product was further purified by dissolving the product in ethyl acetate and then precipitating impurities with addition of hexanes, giving 94 mg (36%) of complex. The product is sufficiently soluble in hexanes. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.57-7.41 (m, 2H), 7.39-7.08 (m, 8H), 6.58-6.40 (m, 1H), 6.26 (td, *J* = 3.2, 6.9 Hz, 1H), 5.20-5.01 (m, 1H), 4.89 (br s, 1H), 4.41-4.20

(m, 1H), 3.77-3.54 (m, 2H), 3.54-3.34 (m, 2H), 3.34-3.11 (m, 4H), 3.02 (dd, *J* = 4.4, 13.5 Hz, 1H), 2.77 (dd, *J* = 10.4, 13.6 Hz, 1H), 2.70-2.54 (m, 2H), 2.54-2.22 (m, 4H), 2.19-1.57 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 218.9, 218.3, 161.6, 139.8, 139.4, 138.9, 130.0, 129.9, 129.4, 128.8, 128.5, 128.3, 126.8, 126.3, 126.2, 97.5, 97.4, 97.3, 69.7, 69.4, 68.5, 68.1, 66.7, 66.5, 59.6, 52.2, 52.0, 50.3, 42.1, 40.9, 40.8, 33.2, 32.9, 30.7, 29.9, 29.0, 28.7, 28.1, 26.6, 25.5, 24.8, 23.2. HRMS (*m*/*z*): $[M - Cl]^+$ calcd for $C_{31}H_{40}ClN_2Rh$, 543.2241; found, 543.2248.

Suzuki cross-coupling reaction

1-Naphthylboronic acid (46.4 mg, 0.269 mmol), 1-bromo-2-methoxynaphthalene (52.4 mg, 0.221 mmol), palladium complex **3-41** (6.0 mg, 6.6 μmol), and CsF (94.0 mg, 0.619 mmol) were added to a flame dried Schlenk flask. THF (3.5 mL) was added to the solids, and the reaction was heated at reflux for 16 h. After this time, the reaction mixture was diluted with water and extracted with ethyl acetate (3.5 mL x 3). The organic layers were combined, dried with $MgSO_4$, and concentrated. The crude product was purified by column chromatography (hexanes/ethyl acetate, 50:1), resulting in pure biaryl (59.7 mg, 95%). Enantiomeric excess was determined by HPLC analysis using a chiral column (Chiralcel OJ-H; hexane/2-propanol, 4:1; flow rate 1 mL/min; t_R 8.5 and 13.5 min). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.12-7.82 (m, 4H), 7.74-7.58 (m, 1H), 7.55-7.41 (m, 3H), 7.41-7.13 (m, 5H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 154.9, 134.8, 134.5, 134.0, 133.2, 129.7, 129.3, 128.7, 128.5, 128.1, 128.0, 126.6, 126.4, 126.1, 125.9, 125.8, 125.8, 123.8, 123.5, 114.1, 57.0. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{21}H_{16}O$, 284.1196; found, 284.1190.

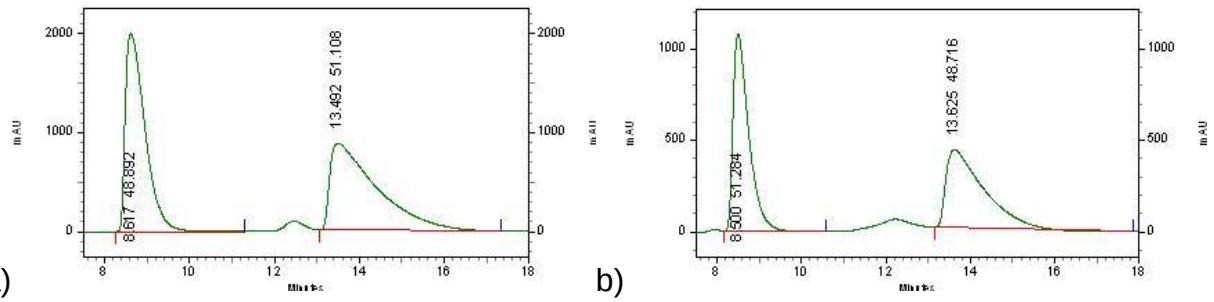
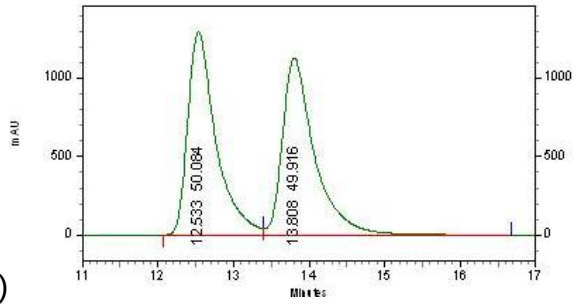


Figure 3-16. HPLC spectra of the Suzuki-Miyaura coupling product a) racemic mixture and b) with **3-41**

1,2-Addition of 1-naphthylboronic acid to *o*-anisaldehyde

To a flame-dried Schlenk flask under argon were added 50.0 mg (0.364 mmol) of *o*-anisaldehyde, 125 mg (0.728 mmol) of 1-naphthylboronic acid, 82.6 mg (0.728 mmol) of potassium *tert*-butoxide, and 2.0 mg (5.2 μmol) of rhodium catalyst **3-42**. Then 1.22 mL of DME and 0.33 mL of water were added, and the solution was heated to 80°C. The mixture was stirred for 1 h and monitored by TLC (R_f 0.38, 4:1 hexanes/ethyl acetate). The solution was diluted with 10 mL of diethyl ether and 10 mL of water and was then extracted three times. The organic layer was dried, concentrated, and then purified by silica gel chromatography (8:1 hexanes/ethyl acetate) to isolate the product as a clear oil (92 mg, 86%yield). Enantiomeric excess was determined by HPLC analysis with a chiral column (Chiralcel IA; hexanes/2-propanol, 9:1; flow rate 1mL/min; t_R12.5 and 13.8min). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.05 (d, *J* = 7.4 Hz, 1H), 7.96-7.79 (m, 2H), 7.71 (d, *J* = 7.1Hz, 1H), 7.60-7.39 (m, 3H), 7.37-7.22 (m, 1H), 7.11-6.78 (m, 4H), 3.91 (s, 3H), 3.22 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 157.2, 138.4, 134.0, 131.6, 131.3, 129.2, 128.9, 128.7, 128.3, 126.2, 125.7, 124.6, 124.5, 121.1, 110.8, 68.6, 55.8. HRMS (*m*/*z*): $[M - OH]^+$ calcd for $C_{18}H_{16}O_2$, 247.1177; found, 247.1176.

a) 

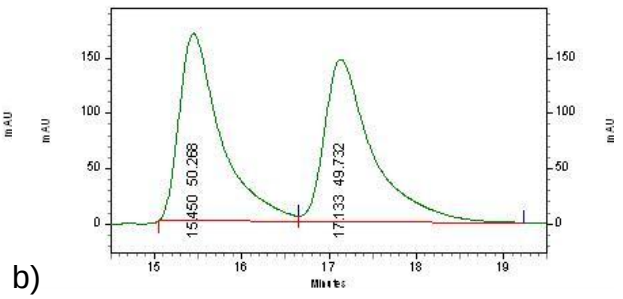
b) 

Figure 3-17. HPLC spectra of the 1,2-addition product a) racemic mixture and b) with **3-42**

CHAPTER 4
CONCLUSION

An improvement of the original design of the isoquinoline-based ligand allowed access to a larger variety of the R substituent (Figure 4-1). The steric and electronic properties could be tuned at a later stage of the preparation. Although ***ent*-2-15dc** gave good enantioselectivity for the β-borylation (85% ee), it did not surpass the one of the original design. Carbene precursor ***ent*-2-15ec**, with its triazole moiety, showed some enantioselectivity in the asymmetric allylic alkylation (up to 45%). An X-ray structure would give precious information about the orientation of the chiral group and certain types of reactions could be targeted from there.

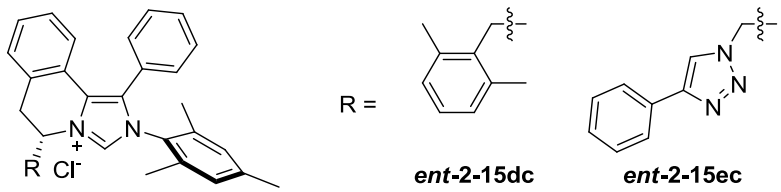
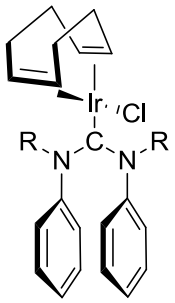


Figure 4-1. New chiral NHC precursors

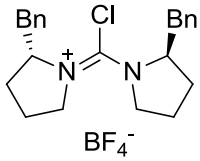
The achiral ADC-iridium complex was successfully obtained (Figure 4-2). Its X-ray structure showed the *syn*-conformation of the carbene as expected and a possible π-π stacking (parallel-displaced). Unfortunately, the catalysis of the hydroboration gave moderate results in terms of regioselectivity (linear/branched: 1/0.58). Therefore, other iridium-catalyzed reactions needed to be tested.

Finally, the chiral ADC ligand precursor was also prepared (Figure 4-3). The drawback of the C-N bond rotation still remained a challenge in order to obtain some enantioselectivity. Again, a wider screening of reactions had to be performed to seek for its potential.



3-22a

Figure 4-2. New ADC-iridium complex **3-22a**



3-40

Figure 4-3. Chiral ADC ligand precursors

LIST OF REFERENCES

(1) Diez-Gonzalez, S. In *N-Heterocyclic Carbenes: From Laboratory Curiosities To Efficient Synthetic Tools.* Silvia Díez-González, Ed.; Royal Society of Chemistry: 2011; , pp 442.

(2) Jacobsen, H.; Correa, A.; Poater, A.; Costabile, C.; Cavallo, L. *Coord. Chem. Rev.* **2009**, *253*, 687-703.

(3) Hoffmann, R. *J. Am. Chem. Soc.* **1968**, *90*, 1475-1485.

(4) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39-92.

(5) Vignolle, J.; Cattoën, X.; Bourissou, D. *Chem. Rev.* **2009**, *109*, 3333-3384.

(6) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.

(7) Hillier, A. C.; Lee, H. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2001**, *20*, 4246-4252.

(8) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804-3805.

(9) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119-122.

(10) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889-9890.

(11) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053-2055.

(12) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729-7737.

(13) Marion, N.; de Frémont, P.; Lemière, G.; Stevens, E. D.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Chem. Commun.* **2006**, 2048-2050.

(14) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225-3228.

(15) Kuhn, K. M.; Bourg, J.; Chung, C. K.; Virgil, S. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 5313-5320.

(16) Tiede, S.; Berger, A.; Schlesiger, D.; Rost, D.; Lühl, A.; Blechert, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 3972-3975.

(17) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7591-7595.

(18) Xu, L.; Shi, Y. *J. Org. Chem.* **2008**, *73*, 749-751.

(19) Luan, X.; Wu, L.; Drinkel, E.; Mariz, R.; Gatti, M.; Dorta, R. *Org. Lett.* **2010**, *12*, 1912-1915.

(20) Luan, X.; Mariz, R.; Robert, C.; Gatti, M.; Blumentritt, S.; Linden, A.; Dorta, R. *Org. Lett.* **2008**, *10*, 5569-5572.

(21) Herrmann, W. A.; Goossen, L. J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed.* **1996**, *35*, 2805-2807.

(22) Wilckens, K.; Lentz, D.; Czekelius, C. *Organometallics* **2011**, *30*, 1287-1290.

(23) Baskakov, D.; Herrmann, W. A.; Herdtweck, E.; Hoffmann, S. D. *Organometallics* **2007**, *26*, 626-632.

(24) Larsen, R. D.; Reamer, R. A.; Corley, E. G.; Davis, P.; Grabowski, E. J. J.; Reider, P. J.; Shinkai, I. *J. Org. Chem.* **1991**, *56*, 6034-6038.

(25) Steinbeck, M.; Frey, G. D.; Schoeller, W. W.; Herrmann, W. A. *J. Organomet. Chem.* **2011**, *696*, 3945-3954.

(26) Albright, A.; Eddings, D.; Black, R.; Welch, C. J.; Gerasimchuk, N. N.; Gawley, R. E. *J. Org. Chem.* **2011**, *76*, 7341-7351.

(27) Kehrli, S.; Martin, D.; Rix, D.; Mauduit, M.; Alexakis, A. *Chem. —Eur. J.* **2010**, *16*, 9890-9904.

(28) Rix, D.; Labat, S.; Toupet, L.; Crévisy, C.; Mauduit, M. *Eur. J. Inorg. Chem.* **2009**, *2009*, 1989-1999.

(29) Sakaguchi, S.; Yoo, K.; O'Neill, J.; Lee, J.; Stewart, T.; Jung, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 9326-9329.

(30) Shibata, N.; Okamoto, M.; Yamamoto, Y.; Sakaguchi, S. *J. Org. Chem.* **2010**, *75*, 5707-5715.

(31) Liu, L.; Wang, F.; Wang, W.; Zhao, M.; Shi, M. *Beilstein J. Org. Chem.* **2011**, *7*, 555-564.

(32) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954-4955.

(33) Cereghetti, M.; Schmid, R.; Schönholzer, P.; Rageot, A. *Tetrahedron Lett.* **1996**, *37*, 5343-5346.

(34) Ma, Y.; Song, C.; Ma, C.; Sun, Z.; Chai, Q.; Andrus, M. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 5871-5874.

(35) Ma, Q.; Ma, Y.; Liu, X.; Duan, W.; Qu, B.; Song, C. *Tetrahedron: Asymmetry* **2010**, *21*, 292-298.

(36) Pye, P.; Rosseen, K.; Volante, R., P. 5,874,629, 1999.

(37) Wiberg, N.; Buchler, J. W. *Z. Naturforsch.* **1964**, *19b*, 953-5.

(38) Wanzlick, H. W.; Schikora, E. *Angew. Chem.* **1960**, *72*, 494-494.

(39) Badley, E. M.; Chatt, J.; Richards, R. L.; Sim, G. A. *J. Chem. Soc. D* **1969**, 1322-1323.

(40) Angelici, R. J.; Charley, L. M. *J. Organomet. Chem.* **1970**, *24*, 205-209.

(41) Bonati, F.; Minghetti, G. *J. Organomet. Chem.* **1973**, *59*, 403-410.

(42) Alder, R. W.; Allen, P. R.; Murray, M.; Orpen, A. G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1121-1123.

(43) Denk, M. K.; Thadani, A.; Hatano, K.; Lough, A. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2607-2609.

(44) Ren, H.; Zhao, X.; Xu, S.; Song, H.; Wang, B. *J. Organomet. Chem.* **2006**, *691*, 4109-4113.

(45) Dubinina, G. G.; Furutachi, H.; Vicic, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 8600-8601.

(46) Arduengo, A. J.; Goerlich, J. R.; Marshall, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11027-11028.

(47) Alder, R.,W.; Blake, M.,E. *Chem. Commun.* **1997**, 1513-1514.

(48) Denk, K.; Sirsch, P.; Herrmann, W. A. *J. Organomet. Chem.* **2002**, *649*, 219-224.

(49) Kremzow, D.; Seidel, G.; Lehmann, C. W.; Fürstner, A. *Chem. —Eur. J.* **2005**, *11*, 1833-1853.

(50) Dhudshia, B.; Thadani, A. N. *Chem. Commun.* **2006**, 668-670.

(51) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290-1309.

(52) Scott, N. M.; Nolan, S. P. *Eur. J. Inorg. Chem.* **2005**, *2005*, 1815-1828.

(53) Glorius, F. In *N-Heterocyclic Carbenes in Catalysis—An Introduction;* Glorius, F., Ed.; N-Heterocyclic Carbenes in Transition Metal Catalysis; Springer Berlin / Heidelberg: 2007; Vol. 21, pp 1-20.

(54) Rosen, E. L.; Sanderson, M. D.; Saravanakumar, S.; Bielawski, C. W. *Organometallics* **2007**, *26*, 5774-5777.

(55) Collins, M. S.; Rosen, E. L.; Lynch, V. M.; Bielawski, C. W. *Organometallics* **2010**, *29*, 3047-3053.

(56) Bartolomé, C.; Carrasco-Rando, M.; Coco, S.; Cordovilla, C.; Martín-Alvarez, J. M.; Espinet, P. *Inorg. Chem.* **2008**, *47*, 1616-1624.

(57) Bartolomé, C.; García-Cuadrado, D.; Ramiro, Z.; Espinet, P. *Inorg. Chem.* **2010**, *49*, 9758-9764.

(58) Hashmi, A. S. K.; Hengst, T.; Lothschütz, C.; Rominger, F. *Adv. Synth. Catal.* **2010**, *352*, 1315-1337.

(59) Hashmi, A. S. K.; Bührle, M.; Wölfle, M.; Rudolph, M.; Wieteck, M.; Rominger, F.; Frey, W. *Chem. —Eur. J.* **2010**, *16*, 9846-9854.

(60) Hashmi, A. S. K.; Lothschütz, C.; Böhling, C.; Rominger, F. *Organometallics* **2011**, *30*, 2411-2417.

(61) Wang, Y.; Kuzniewski, C. N.; Rauniyar, V.; Hoong, C.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 12972-12975.

(62) Handa, S.; Slaughter, L. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 2912-2915.

(63) Seo, H.; Hirsch-Weil, D.; Abboud, K. A.; Hong, S. *J. Org. Chem.* **2008**, *73*, 1983-1986.

(64) Hirsch-Weil, D.; Abboud, K. A.; Hong, S. *Chem. Commun.* **2010**, *46*, 7525-7527.

(65) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568-3571.

(66) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279-3281.

(67) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887-9888.

(68) Jagt, R. B. C.; Toullec, P. Y.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Biomol. Chem.* **2006**, *4*, 773-775.

(69) Duan, H.; Xie, J.; Shi, W.; Zhang, Q.; Zhou, Q. *Org. Lett.* **2006**, *8*, 1479-1481.

(70) Noël, T.; Vandyck, K.; Van der Eycken, J. *Tetrahedron* **2007**, *63*, 12961-12967.

(71) Nishimura, T.; Kumamoto, H.; Nagaosa, M.; Hayashi, T. *Chem. Commun.* **2009**, 5713-5715.

(72) Morikawa, S.; Michigami, K.; Amii, H. *Org. Lett.* **2010**, *12*, 2520-2523.

(73) Yang, X.; Hirose, T.; Zhang, G. *Tetrahedron: Asymmetry* **2009**, *20*, 415-419.

(74) Yu, A.; Cheng, B.; Wu, Y.; Li, J.; Wei, K. *Tetrahedron Lett.* **2008**, *49*, 5405-5407.

(75) Zou, T.; Pi, S.; Li, J. *Org. Lett.* **2009**, *11*, 453-456.

(76) Focken, T.; Rudolph, J.; Bolm, C. *Synthesis* **2005**, *2005*, 429,436-436.

(77) Zhang, R.; Xu, Q.; Zhang, X.; Zhang, T.; Shi, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1928-1935.

(78) Zheng, H.; Zhang, Q.; Chen, J.; Liu, M.; Cheng, S.; Ding, J.; Wu, H.; Su, W. *J. Org. Chem.* **2009**, *74*, 943-945.

(79) Kolychev, E. L.; Shuntikov, V. V.; Khrustalev, V. N.; Bush, A. A.; Nechaev, M. S. *Dalton Trans.* **2011**, *40*, 3074-3076.

(80) Yun, J.; Kim, D.; Yun, H. *Chem. Commun.* **2005**, 5181-5183.

(81) Vilaivan, T. *Tetrahedron Lett.* **2006**, *47*, 6739-6742.

(82) Xiao, H.; Chai, Z.; Zheng, C.; Yang, Y.; Liu, W.; Zhang, J.; Zhao, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 4467-4470.

(83) Ryu, K.; Kim, N. D.; Choi, S. I.; Han, C. K.; Yoon, J. H.; No, K. T.; Kim, K.; Seong, B. L. *Bioorg. Med. Chem.* **2009**, *17*, 2975-2982.

(84) Campbell-Verduyn, L.; Mirfeizi, L.; Dierckx, R. A.; Elsinga, P. H.; Feringa, B. L. *Chem. Commun.* **2009**, 2139-2141.

(85) Abboud, J. M.; Foces-Foces, C.; Notario, R.; Trifonov, R. E.; Volovodenko, A. P.; Ostrovskii, V. A.; Alkorta, I.; Elguero, J. *Eur. J. Org. Chem.* **2001**, *2001*, 3013-3024.

(86) Quagliato, D. A.; Andrae, P. M.; Matelan, E. M. *J. Org. Chem.* **2000**, *65*, 5037-5042.

(87) Cariou, C. A. M.; Kariuki, B. M.; Snaith, J. S. *Org. Biomol. Chem.* **2008**, *6*, 3337-3348.

(88) This work was in collaboration with Dimitri Hirsch-Weil and David Snead and resulted in a joint publication: Hirsch-Weil, D.; Snead, D. R.; Inagaki, S.; Seo, H.; Abboud, K. A.; Hong, S. *Chem. Commun.* **2009**, 2475-2477.

(89) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 15604-15605.

(90) Alexakis, A.; Croset, K. *Org. Lett.* **2002**, *4*, 4147-4149.

(91) Welle, A.; Díez-González, S.; Tinant, B.; Nolan, S. P.; Riant, O. *Org. Lett.* **2006**, *8*, 6059-6062.

(92) Arduengo III, A. J.; Dias, H. V. R.; Davidson, F.; Harlow, R. L. *J. Organomet. Chem.* **1993**, *462*, 13-18.

(93) House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128-3141.

(94) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618-4634.

(95) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701-1703.

(96) Rosen, E. L.; Sung, D. H.; Chen, Z.; Lynch, V. M.; Bielawski, C. W. *Organometallics* **2010**, *29*, 250-256.

(97) Arduengo, A. J. *Acc. Chem. Res.* **1999**, *32*, 913-921.

(98) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210-1250.

(99) McGaughey, G. B.; Gagné, M.; Rappé, A. K. *J. Bio* **1998**, *273*, 15458-15463.

(100) Janiak, C. *J. Chem. Soc., Dalton Trans.* **2000**, 3885-3896.

(101) Woods, W. G.; Strong, P. L. *J. Am. Chem. Soc.* **1966**, *88*, 4667-4671.

(102) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1971**, *93*, 1816-1818.

(103) Kono, H.; Ito, K.; Nagai, Y. *Chem. Lett.* **1975**, 1095-1096.

(104) Männig, D.; Nöth, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 878-879.

(105) Evans, D. A.; Fu, G. C.; Anderson, B. A. *J. Am. Chem. Soc.* **1992**, *114*, 6679-6685.

(106) Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron* **2004**, *60*, 10695-10700.

(107) Aldous, D. J.; Dutton, W. M.; Steel, P. G. *Tetrahedron: Asymmetry* **2000**, *11*, 2455-2462.

(108) Sato, M.; Gunji, Y.; Ikeno, T.; Yamada, T. *Synthesis* **2004**, *2004*, 1434-1438.

(109) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron: Asymmetry* **2003**, *14*, 2625-2632.

(110) Kerr, M. S.; Read, d. A.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725-5728.

(111) Snead, D. R.; Ghiviriga, I.; Abboud, K. A.; Hong, S. *Org. Lett.* **2009**, *11*, 3274-3277.

(112) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366-374.

BIOGRAPHICAL SKETCH

Sébastien Inagaki was born in Cholet, France. After graduating from high school in Cholet (Lycée Sainte-Marie) in 1999, he moved next to Paris (Cergy-Pontoise, France) for his undergraduate study. He obtained a Master degree in organic chemistry from the University of Cergy-Pontoise under the supervision of Professor Thierry Brigaud, in 2005. He also graduated from ESCOM (Ecole Supérieure de Chimie Organique et Minérale) where he obtained a Master degree in chemical engineering, the same year. Sébastien then moved to Gainesville, FL in 2006, to pursue his PhD in organic chemistry at the University of Florida under the supervision of Professor Sukwon Hong. He received his Ph.D. in the spring of 2012.