

DEVELOPMENT OF NI-CATALYZED ASYMMETRIC REDUCTIVE CROSS-
COUPLING REACTIONS

Thesis by

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To my family

ACKNOWLEDGEMENTS

My time at Caltech has been one of the most fortunate and formative times of my life, and it is a place I will fondly remember. The close-knit community of brilliant and supportive students, staff, and faculty makes the challenging work of chemistry possible. I have made many excellent friends here and grown close to tremendous colleagues I look forward to knowing and working with in the future. Caltech is a special place that fosters these relationships and I am lucky to have developed as a scientist here.

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ABSTRACT

Over the last half century, the development of metal-catalyzed cross-coupling reactions has transformed the toolkit of transformations available to synthetic chemists. From the very beginning of this effort, researchers have studied the application of these reactions to afford enantioenriched products via asymmetric catalysis. A great deal of success has been achieved in this arena, giving rise to an ever-growing number of chiral catalysts for a wide range of transformations. Despite these efforts, inherent difficulties in the reactivity of $C(sp^3)$ electrophiles with the most common noble metal catalysts have limited the development of these substrates until more recently. A resurgence of interest in Ni-catalysis has enabled the stereoconvergent cross-coupling of $C(sp^3)$ electrophiles with many partners, opening doors to access these challenging chiral products.

Reductive cross-coupling, involving the union of two different electrophiles, has emerged still more recently, and had previously not been employed asymmetrically. Herein we describe our efforts to develop the first Ni-catalyzed asymmetric reductive cross-couplings of $C(sp^3)$ halides to afford highly enantioenriched products. In the first such reaction, the coupling of acyl chlorides with benzylic chlorides affords acyclic α -tertiary ketone products. Following this, we describe the coupling of new $C(sp^3)$ partners, α -chloronitriles, with challenging Lewis-basic heteroaryl iodides, enabled by the development of a novel PHOX ligand scaffold. Finally, we report the extension of a more general dioxane/TMSCl solvent condition to new asymmetric reductive couplings, including that of heteroaryl iodides with benzylic chlorides, as well as additional preliminary results with new substrate classes.

PUBLISHED CONTENT AND CONTRIBUTIONS

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N.T.K. conducted all reaction development and screening, compilation of data, preparation and evaluation of substrates, and characterization of products. N.T.K. participated in the conception of the project and the writing of the manuscript.

TABLE OF CONTENTS

CHAPTER 1	1
<i>Nickel Catalysis in Cross-Coupling: A Review of Applications in Asymmetric Catalysis and the Rise of Reductive Cross-Coupling</i>	
1.1 INTRODUCTION.....	1
1.2 REACTIONS OF SECONDARY ALKYL ORGANOMETALLIC REAGENTS	5
1.2.1 Organomagnesium Reagents.....	6
1.2.2 Organozinc Reagents.....	12
1.2.3 Organoboron Reagents	14
1.3 REACTIONS OF SECONDARY ALKYL ELECTROPHILES	15
1.3.1 With Organomagnesium Reagents	16
1.3.2 With Organozinc Reagents	17
1.3.3 With Organoboron Reagents.....	24
1.3.4 With Organosilicon Reagents.....	29
1.3.5 With Organozirconium Reagents	30
1.3.6 With Organoindium Reagents.....	31
1.4 TRANSITION METAL-CATALYZED DESYMMETRIZATION REACTIONS.....	31
1.4.1 With Organozinc Reagents	32
1.5 CROSS-ELECTROPHILE COUPLING	34
1.5 CONCLUDING REMARKS	38
1.6 NOTES AND REFERENCES.....	40

CHAPTER 2	46
<i>Catalytic Asymmetric Reductive Acyl Cross-Coupling: Synthesis of Enantioenriched Acyclic α,α-Disubstituted Ketones</i>	
2.1 INTRODUCTION.....	46
2.2 REACTION DEVELOPMENT.....	53
2.3 SUBSTRATE SCOPE.....	65
2.4 CONCLUDING REMARKS	70
2.5 EXPERIMENTAL SECTION.....	71
2.5.1 Materials and Methods.....	71
2.5.2 Substrate Synthesis.....	72
2.5.3 Enantioselective Reductive Cross-Coupling.....	74
2.5.4 SFC Traces of Racemic and Enantioenriched Ketone Products	93
2.6 NOTES AND REFERENCES	114
APPENDIX 1	116
Spectra Relevant to Chapter 2	
CHAPTER 3	169
<i>Nickel-Catalyzed Asymmetric Reductive Cross-Coupling Between Heteroaryl Iodides and α-Chloronitriles</i>	
3.1 INTRODUCTION.....	169
3.2 REACTION DEVELOPMENT.....	173
3.3 SUBSTRATE SCOPE.....	182
3.4 MECHANISTIC STUDIES.....	197
3.5 CONCLUDING REMARKS	199

3.6 EXPERIMENTAL SECTION.....	200
3.6.1 Materials and Methods.....	200
3.6.2 Ligand and Substrate Preparation	201
3.6.3 Enantioselective Reductive Cross-Coupling.....	212
3.6.4 Derivatization of Enantioenriched Nitrile Products.....	233
3.6.5 SFC Traces of Racemic and Enantioenriched Ketone Products	237
3.7 NOTES AND REFERENCES	263
 APPENDIX 2	 265
Spectra Relevant to Chapter 3	
 CHAPTER 4	 354
<i>Nickel-Catalyzed Asymmetric Reductive Cross-Coupling to Access 1,1-Di(hetero)arylalkanes</i>	
 4.1 INTRODUCTION.....	 354
4.1.1 Background and Catalytic Asymmetric Approaches	354
4.1.2 Reductive Cross-Coupling Approaches and Preliminary Investigations	356
4.1.3 Reaction Design: Substrate and Condition Considerations	359
 4.2 REACTION DEVELOPMENT.....	 361
4.2.1 Ligand Exploration and Condition Optimization	361
4.2.2 Substrate Scope and Disconnection Strategy	368
 4.3 MECHANISTIC INVESTIGATIONS.....	 372
 4.4 CONCLUDING REMARKS	 376
 4.5 EXPERIMENTAL SECTION.....	 376
4.5.1 Materials and Methods.....	376
4.5.2 Ligand Preparation.....	378

4.5.3 Substrate Preparation	383
4.5.4 Enantioselective Reductive Cross-Coupling.....	386
4.5.5 Mechanistic Experiments	402
4.5 NOTES AND REFERENCES	406
 APPENDIX 3	 408
Spectra Relevant to Chapter 4	
 CHAPTER 5	 456
<i>Preliminary Results Toward Novel Ni-Catalyzed Asymmetric Reductive Cross-Couplings</i>	
 5.1 INTRODUCTION.....	 456
5.2 VINYLATION OF CHLORONITRILES	459
5.3 COUPLING OF BENZYL CHLORIDES WITH CHLOROPHOSPHINES.....	462
5.4 COUPLING OF (HETERO)ARYL IODIDES AND CHLOROESTERS	465
5.5 CONCLUDING REMARKS	468
5.6 EXPERIMENTAL SECTION.....	469
5.6.1 Materials and Methods.....	469
5.6.2 Vinyl iodide/α-Chloronitrile Cross-Coupling	470
5.6.3 Chlorophosphine/Benzyl Chloride Cross-Coupling	470
5.6.4 (Hetero)aryl Iodide/α-Chloroester Cross-Coupling	471
5.7 NOTES AND REFERENCES	472
ABOUT THE AUTHOR.....	473

LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
Ac	acetyl
acac	acetylacetone
'Am	<i>tert</i> -amyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
bathophen	bathophenanthroline
BBN	borabicyclo[3.3.1]nonane
BHT	2,6-di- <i>tert</i> -butyl-4-methylphenol (“ <u>butylated hydroxytoluene</u> ”)
Biox	bi(oxazoline)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi(2-naphthol)
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Box	bis(oxazoline)
bp	boiling point
BPPFA	<i>N,N</i> -dimethyl-1-[1',2-bis(diphenylphosphino)ferrocenyl]ethylamine
br	broad

Bu	butyl
ⁱ Bu	<i>iso</i> -butyl
ⁿ Bu	butyl or <i>norm</i> -butyl
^s Bu	<i>sec</i> -butyl
^t Bu	<i>tert</i> -butyl
Bz	benzoyl
c	concentration of sample for measurement of optical rotation
°C	degrees Celsius
calc'd	calculated
CAM	cerium ammonium molybdate
cm ⁻¹	wavenumber(s)
cod	1,5-cyclooctadiene
conc.	concentrated
Cp	cyclopentadienyl
Cy	cyclohexyl
Cyp	cyclopentyl
d	doublet
<i>d</i>	dextrorotatory
D	deuterium
dba	dibenzylideneacetone
DFT	density functional theory
DIOP	2,3- <i>O</i> -isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

DKR	dynamic kinetic resolution
DMA	<i>N,N</i> -dimethylacetamide
DMBA	2,6-dimethylbenzoic acid
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMPU	<i>N,N'</i> -dimethylpropylene urea
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppbz	1,2-bis(diphenylphosphino)benzene
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereomeric ratio
dtbpy	4,4'-di- <i>tert</i> -butyl-2,2'-bipyridine
DYKAT	dynamic kinetic asymmetric transformation
<i>E</i>	trans (entgegen) olefin geometry
ee	enantiomeric excess
EI	electron impact
EPPF	1-diphenylphosphino-2-ethylferrocene
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
FcPN	1-dimethylaminomethyl-2-diphenyl-phosphinoferrocene

g	gram(s)
GC	gas chromatography
h	hour(s)
^1H	proton
hex	hexyl
HMDS	hexamethyldisilazane
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IPA	isopropanol
IR	infrared spectroscopy
J	coupling constant
k	rate constant
L	liter or neutral ligand
l	levorotatory
LED	light-emitting diode
m	multiplet or meter(s)
M	molar or molecular ion
m	meta
Me	methyl
mg	milligram(s)
MHz	megahertz

min	minute(s)
mL	milliliter(s)
MM	mixed method
mol	mole(s)
MOP	2-(diphenylphosphino)-2'-methoxy-1,1'-binaphthyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves or mass spectrometry
<i>m/z</i>	mass-to-charge ratio
naph	naphthyl
Naphos	2,2'-bis(diphenylphosphinomethyl)-1,1'-binaphthyl
nbd	norbornadiene
NBS	<i>N</i> -bromosuccinimide
NMDPP	neomenthyldiphenylphosphine
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Norphos	2,3-bis(diphenylphosphino)-bicyclo[2.2.1]hept-5-ene
<i>o</i>	ortho
<i>p</i>	para
Pc	phthalocyanine
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
phen	1,10-phenanthroline

PHOX	phosphinooxazoline
pin	pinacol
Piv	pivaloyl
pK_a	acid dissociation constant
PPFA	<i>N,N</i> -dimethyl-1-[2-(diphenylphosphino)ferrocenyl]ethylamine
Pr	propyl
ⁱ Pr	isopropyl
ⁿ Pr	propyl or <i>norm</i> -propyl
Prophos	1,2-bis(diphenylphosphino)propane
py	pyridine
PyBox	pyridine-bis(oxazoline)
PyOx	pyridine-oxazoline
pyphos	(2-diphenylphosphino)ethylpyridine
q	quartet
Quinox	quinoline-oxazoline
R	alkyl group
<i>R</i>	rectus
ref	reference
R_f	retention factor
rt	room temperature
s	singlet or seconds
<i>S</i>	sinister
sat.	saturated

SET	single-electron transfer
SFC	supercritical fluid chromatography
t	triplet
TADDOL	$\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAB	tetra- <i>n</i> -butylammonium bromide
TBAI	tetra- <i>n</i> -butylammonium iodide
TBAT	tetra- <i>n</i> -butylammonium difluorotriphenylsilicate
TBS	<i>tert</i> -butyldimethylsilyl
TDAE	tetrakis(dimethylamino)ethylene
TFA	trifluoroacetic acid
temp	temperature
terpy	2,2':6',2''-terpyridine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	toluene
UV	ultraviolet
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry