DEVELOPMENT OF NICKEL-CATALYZED ASYMMETRIC REDUCTIVE CROSS-COUPLING OF BENZYLIC ELECTROPHILES

Thesis by

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To my teachers

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The five years I have spent at the California Institute of Technology have been a transformational experience because of both the research I have been immersed in and the talented people that surrounded me. Caltech is truly a unique environment that I will remember fondly as I move on in my career.

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ABSTRACT

Over the last forty years, the advent of transition metal-catalyzed cross-coupling has revolutionized the synthetic chemist's ability to generate C–C bonds. Since the 1970s, a parallel effort to control the stereochemical outcome of such transformations has yielded a variety of chiral catalyst complexes that deliver enantioenriched cross-coupled products. Nonetheless, challenges in the use of C(sp^3)-hybridized coupling partners have limited asymmetric variants to a narrow fraction of the total number of cross-coupling methodologies published each year.

Herein, we report studies on the asymmetric cross-coupling of benzylic groups under either Pd or Ni catalysis. We have developed a Pd-catalyzed Fukuyama cross-coupling of thioesters and secondary benzylzinc halides to deliver racemic ketones under mild conditions. Investigations with chiral catalysts revealed that a promising asymmetric transformation could be achieved to give modestly enantioenriched ketones.

Reductive cross-coupling, involving the union of two different electrophiles, has the added advantage of avoiding harsh or expensive organometallic reagents. We have discovered the first highly enantioselective Ni-catalyzed reductive cross-couplings of two organohalide electrophiles. Treatment of an acid chloride and a secondary benzyl chloride with a chiral nickel/bis(oxazoline) complex and Mn^0 as the stoichiometric reductant furnishes ketone products in good yield and high enantioselectivity. Expanding on this result, we have demonstrated that vinyl bromides and secondary benzyl chlorides can be cross-coupled using a different chiral nickel/bis(oxazoline) complex, illustrating the generality of an asymmetric reductive coupling platform. Preliminary studies directed toward other coupling partners are also disclosed.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
Ac	acetyl
acac	acetylacetonate
^{t}Am	*tert*-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-*tert*-butyl-4-methylphenol ("butylated hydroxytoluene")
Biox	bi(oxazoline)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi(2-naphthol)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Box	bis(oxazoline)
bp	boiling point
BPPFA	*N*,*N*-dimethyl-1-[l',2-bis(diphenylphosphino)ferrocenyl]ethylamine
br	broad

Bu	butyl
^{i}Bu	*iso*-butyl
^{n}Bu	butyl or *norm*-butyl
^{s}Bu	*sec*-butyl
^{t}Bu	*tert*-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
d	dextrorotatory
D	deuterium
dba	dibenzylideneacetone
DFT	density functional theory
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

DKR	dynamic kinetic resolution
DMA	*N*,*N*-dimethylacetamide
DMBA	2,6-dimethylbenzoic acid
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMPU	*N*,*N*'-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-*tert*-butyl-2,2'-bipyridine
DYKAT	dynamic kinetic asymmetric transformation
E	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	l-dimethylaminomethyl-2-diphenyl-phosphinoferrocene

g	gram(s)
GC	gas chromatography
h	hour(s)
^{1}H	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
m/z	mass-to-charge ratio
naph	naphthyl
Naphos	2,2'-bis(diphenylphosphinomethy1)-1,1'-binaphthyl
nbd	norbornadiene
NBS	*N*-bromosuccinimide
NMDPP	neomenthyldiphenylphosphine
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Norphos	2,3-bis(diphenylphosphino)-bicyclo[2.2.1]hept-5-ene
o	ortho
p	para
Pc	phthalocyanine
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
phen	1,10-phenanthroline

pin	pinacol
Piv	pivaloyl
pK_a	acid dissociation constant
PPFA	*N*,*N*-dimethyl-1-[2-(diphenylphosphino)ferrocenyl]ethylamine
Pr	propyl
^{i}Pr	isopropyl
^{n}Pr	propyl or *norm*-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
R	rectus
ref	reference
R_f	retention factor
rt	room temperature
s	singlet or seconds
S	sinister
sat.	saturated
SET	single-electron transfer

SFC	supercritical fluid chromatography
t	triplet
TADDOL	α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAB	tetra-*n*-butylammonium bromide
TBAI	tetra-*n*-butylammonium iodide
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBS	*tert*-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	*N*,*N*,*N*',*N*'-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