DEVELOPMENT OF NICKEL-CATALYZED ASYMMETRIC REDUCTIVE CROSS-COUPLING REACTIONS

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To my family, gifted and gained

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ABSTRACT

Asymmetric reductive cross-electrophile coupling is a powerful method to forge C–C bonds and access enantioenriched small molecules, which can be further functionalized to access scaffolds present in natural products and bioactive pharmaceutical agents. However, an innate challenge of this methodology is identifying a chiral catalyst that achieves optimal cross-selectivity and stereocontrol. Herein, we report studies on the asymmetric cross-coupling of $C(sp^3)$ electrophiles, such as benzyl chlorides, α-chloroesters, and *N*-hydroxyphthalimide esters, with several classes of $C(sp^2)$ electrophiles.

We describe the asymmetric Ni-catalyzed reductive cross-coupling of (hetero)aryl iodides and benzyl chlorides to prepare enantioenriched 1,1-diarylalkanes. As part of these studies, a new chiral bi(oxazoline) ligand, 4-HeptylBiOX, was developed to obtain products in synthetically useful yield and enantioselectivity. This novel ligand is demonstrated to expand the substrate scope of these stereoconvergent reductive cross-couplings to include the asymmetric cross-coupling of α-chloroesters with aryl iodides, and sterically hindered *N*-hydroxyphthalimide esters with alkenyl bromides. Model studies have been initiated to study the application of these reactions toward the total synthesis of cylindrocyclophane natural products.

PUBLISHED CONTENT AND CONTRIBUTIONS

Portions of the work described herein were disclosed in the following communications:

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
Ac	acetyl
acac	acetylacetonate
alk	alkyl
^{t}Am	*tert*-amyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl
atm	atmosphere(s)
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
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
^{13}C	carbon-13 isotope
/C	supported on activated carbon charcoal
°C	degrees Celsius
calc'd	calculated
CAM	cerium ammonium molybdate
cat.	catalyst
Cbz	benzyloxycarbonyl
cf.	consult or compare to (Latin: *confer*)
cis	on the same side
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
conc.	concentrated
conv.	conversion
Cp	cyclopentadienyl
Cy	cyclohexyl
Cyp	cyclopentyl

Δ	heat or difference
δ	chemical shift in ppm
d	doublet
d	deutero or dextrorotatory
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DIPEA	*N*,*N*-diisopropylethylamine
DIBAL	diisobutylaluminum hydride
DFT	density functional theory
DKR	dynamic kinetic resolution
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
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	methyl carboxylate (CO_2CH_3)
E^+	electrophile
E	trans (entgegen) olefin geometry
EDCI	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
epi	epimeric
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
FAB	fast atom bombardment
g	gram(s)
GC	gas chromatography
h	hour(s)
^1H	proton
[H]	reduction
HC	homocoupling

hex	hexyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: *id est*)
in situ	in the reaction mixture
IPA	isopropanol
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
LC/MS	liquid chromatography–mass spectrometry
LDA	lithium diisopropylamide
LED	light-emitting diode
m	multiplet or meter(s)

M	molar or molecular ion
m	meta
μ	micro
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves or mass spectrometry
m/*z*	mass-to-charge ratio
naph	naphthyl
nbd	norbornadiene
NBS	*N*-bromosuccinimide
ND	not determined
NHC	*N*-heterocyclic carbene
NHP	*N*-hydroxyphthalimide
nm	nanometer(s)

NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o	ortho
[O]	oxidation
p	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
Pr	propyl
^{i}Pr	isopropyl
^{n}Pr	propyl or *norm*-propyl
py	pyridine
PyBOX	pyridine-bis(oxazoline)
PyOx	pyridine-oxazoline
pyphos	(2-diphenylphosphino)ethylpyridine
q	quartet
quant.	quantitative
QuinOx	quinoline-oxazoline

R	alkyl group
R_L	large group
R	rectus
RCM	ring-closing metathesis
recry.	recrystallization
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
SM	starting material
t	triplet
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBS	*tert*-butyldimethylsilyl
TDAE	tetrakis(dimethylamino)ethylene
Tf	trifluoromethanesulfonyl
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
trans	on the opposite side
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
vide infra	see below
v/v	volume per volume
w/v	weight per volume
X	anionic ligand or halide
xs	excess
Y	anionic ligand or halide
Z	cis (zusammen) olefin geometry