SYNTHETIC APPLICATIONS AND METHODOLOGICAL DEVELOPMENTS OF DONOR–ACCEPTOR CYCLOPROPANES

Thesis by

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To my teachers

ACKNOWLEDGEMENTS

In Pirkei Avot, a prominent collection of Jewish ethics and morals, Shimon ben Zoma is quoted: "Who is wise? He who learns from all people." This phrase has been somewhat of a guiding principle for me throughout my graduate studies, and throughout my time at Caltech I have been surrounded by an incredible group of people. These are the many students, professors and staff who have contributed toward my development as a scientist and have provided me with plenty of lessons in life and in Chemistry. I have resigned myself to the knowledge that this section will invariably be inadequate to address every manner in which I have been changed for the better by my interactions at this singular institution.

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Alex

ABSTRACT

Donor–acceptor cyclopropanes are a versatile class of synthetic intermediates, compatible in a broad range of ring-opening reactions and formal cycloadditions, and employed in numerous natural product syntheses. We have developed new Lewis acid mediated cycloadditions for the synthesis of five-membered heterocycles, and applied existing a transition metal catalyzed cyclopropane cycloaddition method toward the synthesis of complex alkaloids.

First, described is the development of a Lewis acid mediated (3 + 2) cycloaddition of donor–acceptor cyclopropanes with isocyanates, isothiocyanates and carbodiimides. This reaction was found in certain cases to proceed with excellent stereochemical fidelity, providing access to an array of enantioenriched thioimidates and amidines.

Second, we targeted the *Melodinus* alkaloids for total synthesis due to their unique structural features. Synthetic efforts toward scandine, the parent of the natural product family, are detailed herein. Our approach features a palladium catalyzed formal (3 + 2) cycloaddition of a vinyl cyclopropane and a β-nitrostyrene to rapidly assemble the central cyclopentane core of the natural product. Initial efforts focused on the synthesis and application of a 1,1-divinylcyclopropane to the formal (3 + 2) cycloaddition reaction, whereas later work entailed the use of a mono-vinylcyclopropane with the goal of installing the second requisite vinyl group at a later stage using modern C–H functionalization technologies.

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LIST OF ABBREVIATIONS

Å	Ångstrom
$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl
Anal.	combustion elemental analysis
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
atm	atmosphere
BBN	borabicyclononane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl
t-Bu	*tert*-Butyl
Bz	benzoyl
c	concentration for specific rotation measurements
°C	degrees Celsius
ca.	about (Latin circa)
calc'd	calculated

CAN	ceric ammonium nitrate
cat	catalytic
Cbz	carbobenzyloxy
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	compare (Latin confer)
CI	chemical ionization
CID	collision-induced dissociation
cm^{-1}	wavenumber(s)
comp	complex
Cy	cyclohexyl
d	doublet
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
dec	decomposition
DIAD	diisopropyl azodicarboxylate
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
dmdba	bis(3,5-dimethoxybenzylidene)acetone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	(deoxy)ribonucleic acid
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio

E_A	activation energy
EC_{50}	median effective concentration (50%)
EDC	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide
ee	enantiomeric excess
EI	electron impact
e.g.	for example (Latin exempli gratia)
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
FID	flame ionization detector
g	gram(s)
GC	gas chromatography
gCOSY	gradient-selected correlation spectroscopy
GlyPHOX	2-(2-(diphenylphosphino)phenyl)oxazoline
h	hour(s)
HIV	human immunodeficiency virus
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSV	herpes simplex virus
$h\nu$	light
Hz	hertz
IC_{50}	median inhibition concentration (50%)
i.e.	that is (Latin id est)

IR	infrared (spectroscopy)
J	coupling constant
kcal	kilocalorie
KDA	potassium diisopropylamide
KHMDS	potassium hexamethyldisilazide
λ	wavelength
L	liter
LDA	lithium diisopropylamide
lit.	literature value
LTQ	linear trap quadrupole
m	multiplet; milli
m	meta
m/*z*	mass to charge ratio
M	metal; molar; molecular ion
Me	methyl
MHz	megahertz
μ	micro
μwaves	microwave irradiation
min	minute(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
n	nano
N	normal

nbd	norbornadiene
NBS	*N*-bromosuccinimide
NIST	National Institute of Standards and Technology
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu	nucleophile
[O]	oxidation
o	ortho
p	para
PA	proton affinity
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
PhMe	toluene
PHOX	phosphinooxazoline
Piv	pivaloyl
p*Ka*	p*K* for association of an acid
PMB	*p*-methoxybenzyl
pmdba	bis(4-methoxybenzylidene)acetone
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl

Py	pyridine
q	quartet
ref	reference
R	generic for any atom or functional group
R_f	retention factor
rt	room temperature
s	singlet or strong or selectivity factor
sat.	saturated
SET	single electron transfer
S_N2	second-order nucleophilic substitution
sp.	species
t	triplet
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TCDI	1,1'-thiocarbonyldiimidazole
TCNE	tetracyanoethylene
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
Tol	tolyl

TON	turnover number
t_R	retention time
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
v/*v*	volume to volume
w	weak
w/*v*	weight to volume
X	anionic ligand or halide