THE ADAPTIVE NATURE OF PALLADIUM REACTIVITY IN SYNTHESIS

Thesis by

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To my family

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ABSTRACT

Both Pd(0) and Pd(II) have had, and continue to have, far-reaching impacts on organic synthesis. The versatile nature of palladium, in conjunction with the mechanistic understanding and predictive models that have been elucidated, has permitted a wealth of exploration into the seemingly endless potential of this metal. The utility of palladium is described in the context of the syntheses of the pharmaceutical agents Prozac® and Singulair®, as well as the natural products dragmacidin F and telomestatin.

First, the palladium-catalyzed aerobic oxidative kinetic resolution for the enantioselective preparation of a variety of pharmaceutical substances, including Prozac® and Singulair®, is described. In this regard, the versatility of this resolution is further demonstrated by the diversity of the substrates chosen for this study, and for the first time this work extends the utility of the resolution to include amino alcohol derivatives and highly functionalized benzylic alcohols.

Secondly, an enantiodivergent strategy for the total chemical synthesis of both (+)- and (–)-dragmacidin F from a single enantiomer of quinic acid has been developed and successfully implemented. Although unique, the synthetic routes to these antipodes share a number of key features, including novel Pd(0) reductive isomerization reactions, Pd(II)-mediated oxidative carbocyclization reactions, halogen-selective Suzuki couplings, and high-yielding late-stage Neber rearrangements.

Finally, progress toward the total synthesis of the potent telomerase inhibitor telomestatin is described. Palladium-mediated cross-coupling reactions are employed to assemble oligooxazole intermediates from oxazole building blocks. Additionally, this strategy utilizes a minimum number of protecting groups, and proposes a unique aryl–aryl macrocyclization as the last step of the synthesis. In addition to the biological relevance of the desired target, a successful total synthesis of telomestatin would also enable rapid access to the preparation of telomestatin analogs. This would allow for the investigation of key interactions between telomestatin and the G-quadruplex.

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LIST OF ABBREVIATIONS

Å	Ångstrom
$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl, acetate
app.	apparent
aq.	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOXAX	2,2'-Bis(oxazolyl)-1,1'-binaphthyl
bp	boiling point
BQ	benzoquinone
br	broad
Bu	butyl
n-Bu	butyl
t-Bu	*tert*-Butyl
c	concentration for specific rotation measurements
°C	degrees Celsius
calc'd	calculated
cat.	catalytic
Cbz	carbobenzyloxy
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
CI	chemical ionization

comp.	complex
Cy	cyclohexyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
dba	dibenzylideneacetone
dec.	decomposition
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	(deoxy)ribonucleic acid
dr	diastereomeric ratio
EC_{50}	median effective concentration (50%)
EDC	*N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
g	gram(s)
GC	gas chromatography
gCOSY	gradient-selected correlation spectroscopy
h	hour(s)

HIV	human immunodeficiency virus
HMDS	1,1,1,3,3,3-hexamethyldisilazane
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%)
IR	infrared (spectroscopy)
J	coupling constant
λ	wavelength
L	liter
m	multiplet or milli
m	meta
m/z	mass to charge ratio
μ	micro
M	metal or molar
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
n	nano
N	normal

nbd	norbornadiene
NBS	*N*-bromosuccinimide
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
PDC	pyridinium dichromate
Pin	pinacolato
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
ppm	parts per million
PPTs	pyridinium *p*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
Py	pyridine
q	quartet
ref	reference
R_f	retention factor
rt	room temperature
s	singlet or strong or selectivity factor
sat.	saturated
SEM	(trimethylsilyl)ethoxymethyl

SET	single electron transfer
sp	species or (–)-sparteine
t	triplet
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TCNE	tetracyanoethylene
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TON	turnover number
Tr	trityl
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
w	weak
w/*v*	weight to volume
v/*v*	volume to volume
X	anionic ligand or halide