

**Development of Enantioselective Organocatalytic Technologies for
the Alpha-functionalization of Aldehydes and Ketones**

Thesis by

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To Dad

for all your love, support and encouragement that enabled me to achieve my dreams

and

Tony

*pour toute la joie et le bonheur que tu apportes à ma vie qui font passer les jours avec
douceur, et qui rend possible la poursuite de tous les désires de mon coeur*

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Abstract

The development of an expeditious and room-temperature conversion of aliphatic aldehydes to chiral terminal epoxides is described. α -Chloroaldehydes were prepared via asymmetric enamine catalysis with an imidazolidinone catalyst followed by *in situ* reduction and cyclization to generate the terminal epoxide. Epoxides with a variety of aliphatic groups and functionalities were produced in 75 minutes with good yields and excellent selectivities.

The catalytic enantioselective direct α -fluorination of aldehydes and ketones is also reported. α -Fluoroaldehydes were conveniently prepared via enamine catalysis with an imidazolidinone catalyst and *N*-fluorobenzenesulfonimide (NFSI) as an electrophilic fluorine source. The method tolerated a wide variety of aldehyde substrates and functional groups. Catalyst loadings as low as 1 mol% generated the fluorinated products in good yield and excellent enantioselectivity. Additionally, various catalyst architectures were studied to apply the α -fluorination reaction to ketone substrates. Cinchona alkaloid-derived catalysts were found to successfully facilitate the α -fluorination of ketones in high yields and excellent enantioselectivities.

Also presented is the advent of SOMO catalysis, a new mode of organocatalytic activation based on the catalytic generation of radical cations. A secondary amine catalyst reacts with an aldehyde to transiently generate an enamine that, in turn, undergoes a single-electron oxidation to yield a stabilized radical cation that is subject to enantiofacial discrimination. While the parent enamine reacts only with electrophiles, the radical cation combines with SOMO nucleophiles at the same reacting center, thereby enabling a diverse range of previously unknown asymmetric transformations. As a first example and proof of principle, the development of the direct and enantioselective α -allylation of aldehydes using SOMO catalysis is described.

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List of Abbreviations

AcOH	acetic acid
AIBN	2,2'-azo-bis(isobutyronitrile)
BINAP	2,2'-Bis(diphenylphosphino)-1'1'-binaphthyl
BOC	<i>tert</i> -butyl carbamate
Bn	benzyl
Bz	benzoyl
CA	cinchonine amine
CAN	ceric ammonium nitrate
CDA	cinchonidine amine
dba	dibenzilideneacetone
DBSI	dibenzenesulfonimide
DCA	dichloroacetic acid
DHQA	dihydroquinine amine
DHQDA	dihydroquinidine amine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMS	dimethylsulfide
DNBA	dinitrobenzoic acid
DTBP	di- <i>tert</i> -butyl pyridine
ee	enantiomeric excess
EI	electron impact

ES	electrospray
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atom bombardment
F-TEDA	1-Chloromethyl-4-Fluoro-1,4-Diazoniabicyclo [2.2.2]Octane Bis-(Tetrafluoroborate)
GLC	gas liquid chromatography
HClO₄	perchloric acid
h	hour
HClO₄	perchloric acid
HCN	hydrocyanic acid
HOMO	highest occupied molecular orbital
HMDS	bis(trimethylsilyl)amide
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
IPA	isopropyl alcohol
<i>i</i>-Pr	isopropyl
IR	infrared
LUMO	lowest unoccupied molecular orbital
Me	methyl
MeOH	methanol
min	minutes
MsOH	methanesulfonic acid

NaOEt	sodium ethoxide
NaOMe	sodium methoxide
NMR	nuclear magnetic resonance
NFSI	N-fluorobenzene sulfonimide
OEt	ethoxy
OMe	methoxy
PMB	<i>para</i> -methoxybenzyl
Ph	phenyl
<i>p</i>-TSA	<i>para</i> -toluenesulfonic acid
QA	quinine amine
QDA	quinidine amine
SFC	supercritical fluid chromatography
SOMO	singly occupied molecular orbital
TADDOL	<i>trans</i> - <i>a,a'</i> -(dimethyl-1,3-dioxolane-4,5
TBAF	tetrabutylammonium fluoride
TCA	trichloroacetic acid
TEA	triethyl amine
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
t_r	retention time
vol	volume