MODERN ORGANIC SYNTHESIS IN THE LABORATORY

A COLLECTION OF STANDARD EXPERIMENTAL PROCEDURES

JIE JACK LI
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To Sherry, Rachele, and Mary Kay

For Their Love, Support, and Patience

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Foreword

Those who do not want to imitate anything, produce nothing.
—Salvador Dali

There exists a close analogy between the trials and tribulations of a chemist and those of an artisan. Just as an artist must balance the sensitive interplay of color, light, and brushstroke to create a timeless painting, so too must the chemist carefully marshal the reagents, solvents, and reactions that occupy chemical space to successfully forge a new molecular entity. Finding reliable, standardized procedures for those routine transformations is often a time-consuming and tedious process, one that subtracts from effort that could be devoted towards more creative and exciting pursuits. Indeed, much of the excitement, fascination, and allure of synthetic organic chemistry resides in the imaginative exploration of new realms in chemical reactivity and complexity, not the search for standard operation procedures.

In *Modern Organic Synthesis in the Laboratory*, Drs. Jie Jack Li, Chris Limberakis, and Derek Pflum provide procedures for the common transformations and protocols that permeate the tapestry of synthetic organic chemistry. From guidelines of proper flash chromatography technique, to procedures for drying solvents, and recipes for staining solutions, all of the basic, yet essential, organic laboratory techniques are described in detail. Nearly all types of common reactions for oxidations, reductions, functional group manipulations, and C–C bond formation are covered. With little question, this book is beautifully suited for practitioners of the field at all levels of study because of the thorough selection of procedures and a layout that is both well designed and comprehensive.

We congratulate the authors for filling such an important gap in the chemical literature by carefully designing what will undoubtedly become a survival manual destined for untold numbers of organic chemists.

K. C. Nicolaou and Phil S. Baran
The Scripps Research Institute
July 12, 2006

Preface

The prevalence of computer databases has, at the present time, made literature searching in organic synthesis an increasingly easier enterprise. However, the dilemma has now become how to select one procedure in an ocean of choices. For novices in the laboratory, in particular, this is a daunting task, deciding what reaction conditions to try first in order to have the best chance of success. This collection intends to serve as an "older and wiser" lab-mate by sharing the authors' own experience through this compilation of the most commonly used experimental procedures from established groups and/or rigorously reviewed journals.

Under the title of each experimental procedure, brief commentaries are often offered which summarize the authors' personal experience, and in many instances review articles are cited. These experimental procedures and commentaries are by no means "carved in stone", as you and your lab-mates may have your own favorite protocol. For the final products, detailed spectral data are not given because they simply take up too much space.

We are indebted to Professor John P. Wolfe at the University of Michigan, and his students, Joshua Ney and Josephine Nakhla; Professor Phil S. Baran at the Scripps Research Institute, and his students, Noah Z. Burns, Mike DeMartino, Tom Maimone, Dan O'Malley, Jeremy Richter, and Ryan Shenvi for proofreading the manuscript.

We had a good time putting together these experimental procedures. We have even been using the manuscript ourselves quite often. Hopefully you will find it as useful. We welcome your critique!

Jack Li, Chris Limberakis, and Derek Pflum
Ann Arbor, Michigan
September 4, 2006

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Contents

Abbreviations and Acronyms

	polymer support	BINALH	Lithium 2,2´-dihydroxy-1,1´-binaphthylethoxy-aluminum hydride
Ac	acetyl		
acac	acetylacetonate		
AcOH	acetic acid	BINAP	2,2-bis(diphenylphosphino)-1,1´-binaphthyl
AE	asymmetric epoxidation reaction	BINOL	1,1´-bi-2-naphthol
AIBN	2,2´-azobisisobutyronitrile	BMS	borane dimethyl sulfide complex
Alpine-borane®	*B*-isopinocampheyl-9-borabicyclo[3.3.1]-nonane	Bn	benzyl
		Boc	*tert*-butyloxycarbonyl
		BOM	benzyloxymethyl
AME	acetyl malonic ester	BOP	benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate
AMNT	aminomalononitrile *p*-toluenesulfonate		
Ar	aryl		
B:	generic base	BPO	benzoyl peroxide
9-BBN	9-borabicyclo-[3.3.1]nonane	Bu	butyl
		t-Bu	*tert*-butyl
BFO	benzofurazan oxide	Bz	benzoyl
TBHP	*tert*-butyl hydrogen peroxide	°C	degree Celsius
		CAN	ceric ammonium nitrate (ammonium cerium(IV) nitrate)
BHT	butylated hydroxy toluene		

Chirald®	(2*S*,3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol
CTAB	cetyl trimethylammonium bromide
CBS	Corey–Bakshi–Shibata
Cbz	benzyloxycarbonyl
cp	cyclopentadienyl
CSA	camphorsulfonic acid
CuTC	copper thiophene-2-carboxylate
cy	cyclohexyl
DABCO	1,4-diazabicyclo-[2.2.2]octane
DAPA	dipotassium azodicarboxylate
DAST	(diethylamino)sulfur trifluoride
dba	dibenzylideneacetone
DBE	1,2-dibromoethane
DBU	1,8-diazabicyclo-[5.4.0]undec-7-ene
DBN	1,5-diazabicyclo-[4.3.0]non-5-ene
DCB	dichlorobenzene
DCC	1,3-dicyclohexyl-carbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzo-quinone
de	diastereomeric excess
DEAD	diethyl azodicarboxy-late
DEPC	diethyl phosphoro-cyanidate
DET	diethyl tartrate
Δ	solvent heated under reflux
DHP	dihydropyran
DHPM	3,4-dihydropyrim-idin-2(1*H*)-one
$(DHQ)_2$-PHAL	1,4-bis(9-*O*-dihydroquinine)-phthalazine
$(DHQD)_2$-PHAL	1,4-bis(9-*O*-dihydro-quinidine)-phtha-lazine
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIC	diisopropylcarbo-diimide
Diglyme	diethylene glycol dimethyl ether
Dimsyl	methylsulfinyl-methide
DIPEA	diisopropylethyl-amine
DMAc	*N,N*-dimethyl-acetamide
DMA	*N,N*-dimethylaniline
DMAP	*N,N*-dimethyl-aminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMFDMA	dimethylamino-formaldehyde dimethyl acetal
DMP	Dess-Martin periodinane
DMPU	*N,N´*-dimethyl-*N,N´*-propylene urea
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DMSY	dimethylsulf-oxonium methylide
DMT	dimethoxytrityl
DNP	2,4-dinitrophenyl
L-DOPA	3,4-dihydroxy-phenylalanine
DPPA	diphenylphosphoryl azide
dppb	1,4-bis(diphenylphos-phino)butane
dppe	1,2-bis(diphenylphos-phino)ethane

dppf	1,1´-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
E	Entgegen (opposite, trans)
E1	unimolecular elimination
E2	bimolecular elimination
E1cb	2-step, base-induced β-elimination via carbanion
EDA	ethylendiamine
EDCI	1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride
EDG	electron donating group
EDTA	ethylenediamine tetraacetic acid
ee	enantiomeric excess
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
EMME	ethoxymethylenemalonate
ent	enantiomer
EPP	ethyl polyphosphate
eq	equivalent
Et	ethyl
EtOAc	ethyl acetate
EPR (= ESR)	electron paramagnetic resonance spectroscopy
ESR (= EPR)	electronic spin resonance
EWG	electron withdrawing group
FMO	frontier molecular orbital
Fmoc	9-fluorenylmethoxycarbonyl
FVP	flash vacuum pyrolysis
g	gram(s)
GABA	γ-aminobutyric acid
GC	gas chromatography
glyme	1,2-dimethoxyethane
HOBt	1-hydroxybenzotriazole
h	hour(s)
hν	irradiation with light
His	histidine
HMDS	hexamethyldisilazine
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
IBCF	isobutylchloroformate
IBX	1-Hydroxy-l,2-benziodoxol-3(1*H*)-one
Imd	imidazole
IPA	isopropanol
i-Pr	isopropyl
KHMDS	potassium hexamethyldisilazide
kg	kilogram(s)
K-selectride®	potassium tri-*sec*-butylborohydride
L	liter(s)
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LiHMDS	lithium hexamethyldisilazide
L-selectride®	lithium tri-*sec*-butylborohydride
LTMP	lithium 2,2,6,6-tetramethylpiperidine
LUMO	lowest unoccupied molecular orbital
M	metal
M	moles per liter (molar)
MCR	multi-component reaction
m-CPBA	*m*-chloroperoxybenzoic acid

Me	methyl
MEM	β-methoxyethoxymethyl
Mes	mesitylenyl
MET	methyl ethyl ketone
μg	microgram(s)
μL	microliter(s)
μmol	micromole(s)
mg	milligram(s)
mL	milliliter(s)
mmol	millimole(s)
MMPP	magnesium monoperoxyphthalate hexahydrate
MO	molecular orbital
mol	mole(s)
MOM	methoxymethyl
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MSDS	material safety data sheet
MTBE	methyl *tert*-butyl ether
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
MVK	methyl vinyl ketone
MWI (μν)	microwave irradiation
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMDA	*N*-methyl-D-aspartate
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
Nu	nucleophile
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PDE	phosphodiesterase
PEG	polyethylene glycol
pGlu	pyroglutamic acid
Ph	phenyl
PhFl	9-phenylfluoren-9-yl
phth	phthaloyl
pKa	log acidity constant
PMA	phosphomolybdic acid
PMB	*para*-methoxybenzyl
PPA	polyphosphoric acid
PPE	personal protection equipment
PPE	polyphosphoric ester
4-PPNO	4-phenylpyridine-*N*-oxide
PPP	3-(3-hydroxyphenyl)-1-*n*-propylpiperidine
PPSE	polyphosphoric acid trimethylsilyl ester
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
Pro	proline
psi	pounds per square inch
PTC	phase transfer catalyst
p-TSA	*para*-toluenesulfonic acid
Py or Pyr	pyridine
Ra-Ni	Raney nickel
RCM	ring-closing metathesis
Redal-H	sodium bis(2-methoxyethoxy(aluminum hydride)
ROM	ring-opening metathesis
rt	room temperature
Salen	*N,N′*-disalicylidene-ethylenediamine
SEM	2-(trimethylsilyl) ethoxymethyl
SET	single electron transfer
S_NAr	nucleophilic aromatic substitution
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
t-Bu	*tert*-butyl
TADDOL	α,α,α′,α′-tetraaryl-4,5-dimethoxy-1,3-dioxalane
TASF	$(Et_2N)_3S^+(Me_3SiF_2)^-$
TBAF	tetrabutylammonium fluoride
TBD	1,5,7-triazabicyclo [4.4.0]dec-5-ene

TBDMS or TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TCCA	trichlorocyanuric acid
TCT	2,4,6-trichloro-[1,3,5]-triazine
TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflic)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	trifluoroethanol
TfOH	triflic acid
TFP	tri-*o*-furylphosphine
TFPAA	trifluoro peracetic acid
TFSA	trifluorosulfonic acid
THF	tetrahydrofuran
THP	tetrahydropyran
THIP	4,5,6,7-tetrahydroisoxazolo[5,4-c]-pyridin-3-ol
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N´,N´*-tetramethylethylenediamine
TMG	tetramethylguanidine
TMP	tetramethylpiperidine
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
TMSOTf	trimethylsilyl triflate
Tol	toluene or tolyl
Tol-BINAP	2,2´-bis(di-*p*-tolylphosphino)-1,1´-binaphthyl
TosMIC	(*p*-tolylsulfonyl)methyl isocyanide
TPAP	tetra-*n*-propylammonium perruthenate
Tr	trityl
TRIS	tris(hydroxymethyl) aminomethane
Ts(Tos)	*p*-toluenesulfonyl (tosyl)
TSA	*p*-toluenesulfonic acid
TsO	tosylate
X_c	Chiral auxillary
Z	Zusammen (together, cis)

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